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CLINICAL APPRAISAL OF GROWTH IN CHILDREN

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MEDICAL teaching in the past has devoted scant attention to the nature of growth in the normal child. As a result, few physicians are equipped through their formal training to think accurately in terms of growth. Most often the child's physique is taken for granted, if it is considered at all. The physical examination may start out with the stereotyped phrase, "The patient is a well-developed and well-nourished child of stated age," with no verifying statement as to the child's exact age, height, or weight. The status of the physique frequently is not subjected to any verification or comparison with average standards. Only when deviations from the usual physique are excessive, or when they comprise the entrance complaint, is it customary for the physician to direct his attention toward such careful physical appraisal. In the population at large, he comes into contact with large and with small adults; childhood is considered by him as an indeterminate period during which an individual is small because he is not yet grown, so that to him, the size or degree of development of the child is a matter of little concern.

The physician who is a student of childhood recognizes the fallacy of such a view. The more he works with children, the more intrigued he becomes with observed variations of the pattern of physique and of development. He finds it necessary to keep accurate records of certain physical measurements to serve as a means of following the progress of his patient. He comes to view variations from the average performance critically, and to study the child exhibiting minor deviations from the usual standards to see whether he can learn the cause of his nonconformance. By so doing, he is led to discover certain medical abnormalities which otherwise might have passed undetected.

The following record illustrates the importance of this point. A 9-year-old boy was referred to the pediatric service from the orthopedic

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clinic, to determine whether there were contraindications to operative treatment of knock knees. A diagnosis of postrachitic deformity had been made, and osteotomy was being considered. The youngster was a bright appearing, symmetrically built boy, with no abnormality apparent other than moderate static deformity of the legs and feet. Otherwise, the medical examination was essentially negative. We were about to recommend that the orthopedic treatment be undertaken, when something was mentioned as to the boy's age. Then it was noted that at the age of 9 he was only 44 inches tall, a value which is only par at the age of 6 years. This led at once to the suspicion that the boy's difficulties had remained operative beyond the age characteristic of infantile rickets, and it was considered wise to hospitalize him for further study. That routine led to the discovery of a congenital anomaly of the kidneys with chronic renal insufficiency, which had resulted in renal dwarfism and progressive bony deformity. To have subjected such a patient to operative work would not only have been without value, but in addition, might have proved disastrous.

This raises the question as to acceptable standards of growth. It is evident that the physician cannot depend on his eye and his sense of normality to offer assurance as to a child's degree and rate of growth. In what degree should we expect all children to conform with any arbitrary standards? What are the value and the significance of the standard tables of growth currently available? Granted that the physician has recorded the child's exact age, height, and weight, what means does he have for evaluating these against each other, against predicted values for other children of similar status, or against the child's own propensities for growth? Such knowledge cannot be gained through mere inspection of the child. It is necessary to use reference tables of some form as a guide for judgment. Numerous formulas have been propounded for these purposes. Some of these are as follows:

The majority of infants born at term will weigh from 7 to 7½ pounds; the body length will closely approximate 20 inches (50 cm.), and the circumference of the head will be about 13¾ inches (35 cm.). Under favorable conditions, the infant may double his birth weight in five months or less, triple it by the end of the first year, and quadruple it by the end of the second year. Throughout the period of midchildhood, the average body weight may be approximated roughly by multiplying the age in years by 5 and adding 17, the result being expressed in pounds. The circumference of the head increases most rapidly during the first year, progressively less thereafter. Standard average measurements at 4 months, 8 months, and 1 year are 40 cm., 44 cm., and 45.5 cm., respectively. At 2 years the usual range of observed normal values is from 47 to 50 cm. The usual measurement at 5 years approaches 55 cm., and there is little growth thereafter. As to height, the infant will increase by 50 per cent during the first year of life, will have doubled his birth length by the age of 4, and trebled it by the

age of 13. At the age of 2, he will have reached approximately half of his adult height. From the age of 4 until the acceleration of growth seen at prepuberty, he will grow quite uniformly at the rate of about 2 inches a year.

These values will be found to fit fairly well with clinical observations of the average normal child. Just what is their significance? How were they derived? Can one justifiably assume that any given child will follow a predictable pattern of growth, and what is the significance if he does not?

The foregoing figures and formulas were obtained from the studies of height-weight-age tables similar to those which hang in the offices of most physicians. Those tables, in turn, were developed from anthropometric data obtained from the measurement of large numbers of children by various workers in different parts of this country, as well as abroad. Psychologists have prepared corresponding data relevant to the abilities of children at successive age levels. The authors of these various studies presented them originally as nothing other than cross-sectional values of observed measurements of attainment. These tables have come into use, however, as representative of average attainment, and by implication, as standards of that which is desirable at any age. Many who are engaged in observing the development of children have objected to this perversion of their data. They recognize that, whereas the data were a true expression of what they had found, the figures could not be interpreted as representative of what might be observed under other conditions. A comparative study of average height in terms of age of the child reveals that observed values vary according to when and where the studies were made, whether the children serving as subjects lived in cities or in the country, the socioeconomic level of the families, the preponderant racial groups represented, and still other regards. In general, evidence indicates that, with greater advantage in living conditions, the average trend is toward larger persons at any given age and also in the adult stature. Racial differences seem dependent more on the manner of life than on genetic factors. Studies limited to children living under superior conditions tend to give values greater than the general average, whereas the reverse is observed with children living under handicaps. The general trend in this country indicates that the rate of growth is advancing, and that in addition, the average ultimate height of the adult is increasing.

It is easy to form misconceptions from the studies of averages, however. Such averages do not represent the curve of growth of any individual child; they represent the hypothetical American youngster who is a composite of all his mates, including the more fortunate as well as the less privileged. The degree and nature of dispersion from the average must be taken into consideration. Some growth charts offer not only average values, but the range of values observed and the

degree of distribution of these from the central tendency. Kornfeld, in 1929,[1] reported the range of measurements of children observed by numerous anthropometrists in Europe. For convenience, only measurements of boys are considered. These children were drawn from various socioeconomic levels, representing different ethnic stocks and geographic areas. His average values serve as the background of Fig. 1; with minimal exceptions, all measurements fell within the two outer lines which traverse the diagram. The central tendency showed much less dispersion than these bounds would suggest; two-thirds of the values lay between the two inner solid lines. It will be noted that there is greater dispersion among those measurements which are less than the average than among those which exceed it. With a group of children living under advantageous conditions, the average height at a given age tends to be greater, and in addition, there is lessening of the downward dispersion.

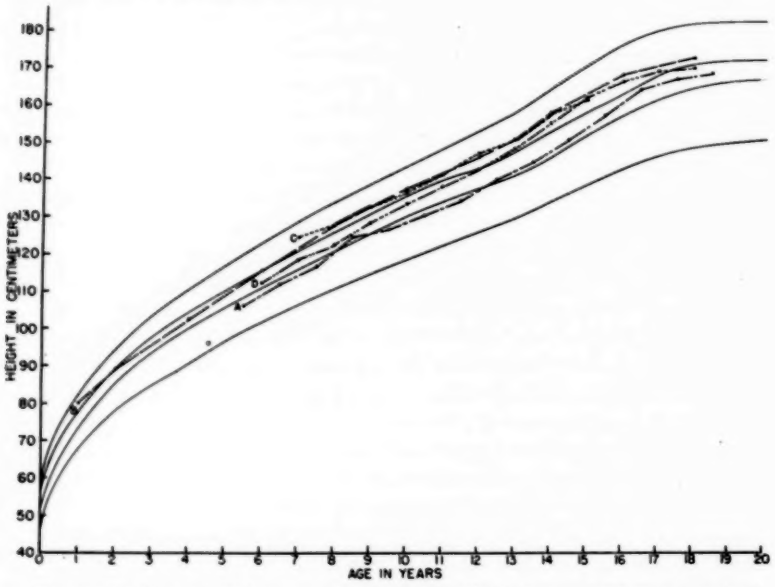

Fig. 1.—Various reported curves of average growth for boys. Solid lines represent range of observed values in study by Kornfeld; the two inner lines include two standard deviations (about two thirds of total values for the corresponding age); the outer lines include four standard deviations, or essentially, all observed measurements. Curves *A*, *B*, *C*, and *D* represent the average values for height at given ages as reported by Boaz, Meredith, Baldwin, and Dearborn and co-workers, respectively (see text).

This tendency toward enhanced growth in favored groups is illustrated by the curves superimposed on Kornfeld's range in Fig. 1, designated *A*, *B*, *C*, and *D*. Curve *A* represents the measurements of a large number of boys, compiled by Boaz and reported in 1898.[2] The subjects were drawn from various parts of the United States and

Canada. Curve *B* is based on cumulative measurements of 1,243 Iowa City boys, collected over a period of fourteen years and reported by Meredith in 1935.[3] Curve *C* represents the measurements of 300 intellectually gifted boys from Terman's study, measured and reported by Baldwin in 1925.[4] Curve *D* is constructed from the measurements of 747 boys, reported from the Harvard growth study in 1938.[5] Several points may be noted. Boaz's study, from values made late in the nineteenth century, correspond quite well with Kornfeld's averages; the other curves are well above his values almost throughout. Most similar to the Boaz data are those from the Harvard study. The majority of the boys in the Harvard study came from the homes of skilled laborers or less skilled workers; a high percentage of the children in Meredith's and Baldwin's studies were from homes of the professional classes. Possibly one is justified to infer that the latter groups may have had some advantages not shared in similar degree by the children from the more humble homes. Many such comparative studies of various groups have been made, and these tend to establish the premise that fortunate living conditions tend to be associated with enhanced growth, and that the current trend is toward higher standards than those accepted as normal a generation ago.[6]

These observations do not fit well with a concept that growth is a process which will go on regardless of what we may do about it. Evidently, under some conditions growth can be depressed, whereas under other circumstances an advance in average growth can be induced. Are we to assume that the children who manifest the trend toward more rapid and greater growth are living under a disadvantage as compared with those who grow more slowly? Such an assumption is difficult to support. Along with this trend toward more rapid growth we find in similar groups a trend toward lower infant mortality, reduction in the incidence of many infectious diseases, improved sanitation, and many other advantageous conditions. As a premise, it seems fair to assume that this trend toward advanced standards of growth is something to be desired for the child population at large. This, however, does not call for enhanced growth for those who already are exhibiting a rate in advance of the average. It calls for efforts to improve conditions for those whose growth is in the lower levels. Let us recognize that our tables of observed rates of growth do not represent standards of *normality;* they represent only the *average.* Where there is a noteworthy tendency toward repression of growth, the average values will be poorer than if these were eliminated from consideration, and consequently will represent a substandard level of attainment. The physician cannot assume that a child is manifesting his optimal rate of growth merely on the premise that his measurements fall within the average observed values. Through recognition of minor interference with optimum growth, the medical attendant may reveal undesirable factors in the child's manner of life, which otherwise might

pass undetected. The following paragraphs and charts offer some growth records which illustrate the effect of various adverse conditions.

Curve *A*, Fig. 2,[7] represents the growth in height of a girl who came to the hospital at the age of 2 years because of fretfulness, poor appetite, and failure to grow. Like the boy who was mentioned previously, this child had chronic kidney disease of an incurable nature. She did not respond favorably to treatment, and died at the age of 8 years. It will be noted that her rate of growth fell off more and more as she approached death. It is not surprising that growth should be impaired in any child with chronic dysfunction of a vital system.

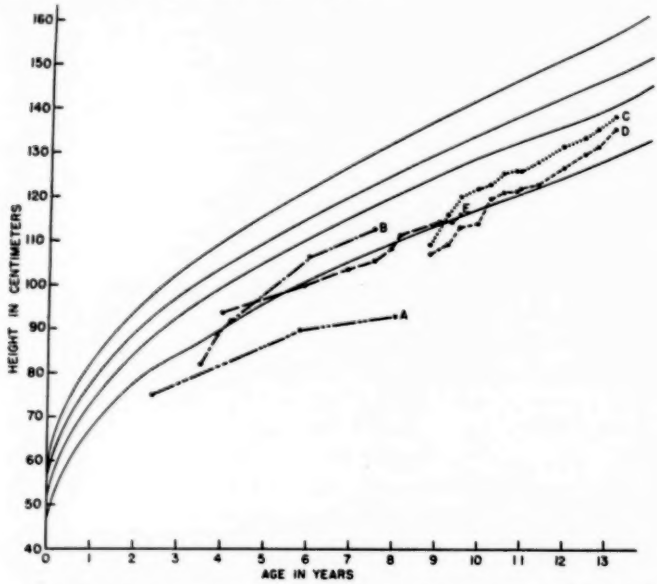

Fig 2.—Growth curves of five children, superimposed on Kornfeld's range of average values. Curves *A*, *B*, *C*, *D*, and *E* represent children with chronic renal insufficiency, celiac disease, diabetes mellitus, the same, and late rickets, respectively. This chart illustrates the capacity for growth in children stunted by disease, when adequate therapy can be maintained.

Retardation of growth may be due to correctable conditions, however. At times it is dependent on undernutrition secondary to socioeconomic limitations, to inadequate therapeutic dietary regimens, or to inability of the child to absorb an adequate diet of the usual composition. Curve B, Fig. 2,[8] illustrates the last mentioned condition. It pictures the growth in height of a boy who was brought to the hospital at the age of 42 months, weighing 16 pounds and measuring only 32 inches in length. His mother stated that he had had diarrhea for most of his life, and that his growth had not been satisfactory since early babyhood. In the hospital he responded well to the regimen of diet prescribed for celiac disease, and his corresponding rate of growth was

phenomenal. During a period of ten weeks he grew 10 cm., and his subsequent growth for several years was in advance of the average. At the age of 7, when he passed out of observation, he almost had attained the normal level for his age.

Growth retardation in the diabetic child is often attributed to the effect of the diabetes mellitus in itself, or to hypothetical associated endocrine dyscrasia. Most frequently it is due to inadequacy of the prescribed dietary regimen. Curves *C* and *D*, Fig. 2,[9] represent the rates of growth of twin girls with diabetes mellitus. The lower of the two curves (*D*) is that of the child whose diabetes became manifest at the age of 3 years; her sister became diabetic five years later. Once the diabetes had been brought under control and the children were able to utilize a diet designed for their needs, they began to grow at an accelerated rate and now have come within the average range of physique.

The effect of another metabolic disturbance on growth is pictured in Curve E, Fig. 2.[10] This represents the growth of a child with intractable late rickets which was controlled only partially through persistent use of enormous amounts of vitamin D daily. It will be noted that the child's rate of growth is normal, but with her metabolic handicap, she does not appear able to accelerate this rate sufficiently to lead her to normal stature.

These examples lead to the conclusion that retarded growth must not be accepted as inevitable, even when associated with chronic illness, unless all available hygienic means have been employed to promote maximum health and normality of function.

Chronic infectious disease seems to exert a depressing effect on growth, even though no specific derangement of function can be demonstrated. Rather often, children with chronic focal infection are undersized as compared with other children in the hospital wards. It is difficult to establish that the infection per se has been responsible for their physical status, for often such children have been underfed as well. However, when indirect measures are used, there is evidence available that chronic infections, even of moderate degree, may serve to depress tissue development throughout the time the infection is active.

Fig. 3 represents growth curves of several infants who were studied under strictly controlled conditions in a metabolism ward while balance studies were being made relevant to the retentions of calcium, phosphorus, and nitrogen. While under observation, these infants developed otitis media which cleared up without mastoidectomy. The oscillations of the height curves, while not unlike those seen frequently in the average infant, are much greater than those seen in the other infants on the metabolism ward who were maintained under the same idealized regimen and who escaped otitis media.[11] More striking and significant as to the effect of the infection on quality of growth is the effect of the infections on the retention of calcium. This is represented in Fig. 4, which contrasts the limits in retention of calcium in the infants with and without

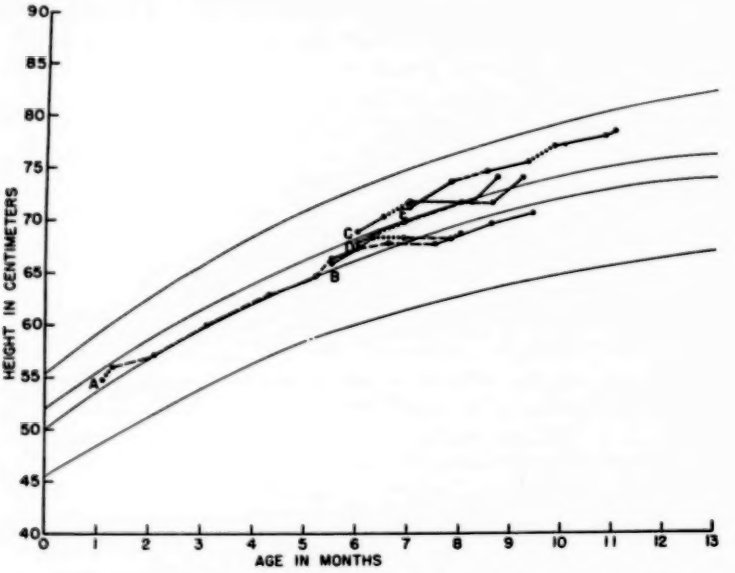

Fig. 3.—Growth curves of five infants with intermittent local infection, superimposed on Kornfeld's range of average values for the first year of life. Dotted lines indicate periods of acute infection (e.g., otitis media); dashed lines represent subacute infection; solid lines indicate intervals free from demonstrable infection. This chart illustrates retarding effect of rather commonplace infectious processes on growth in length during infancy.

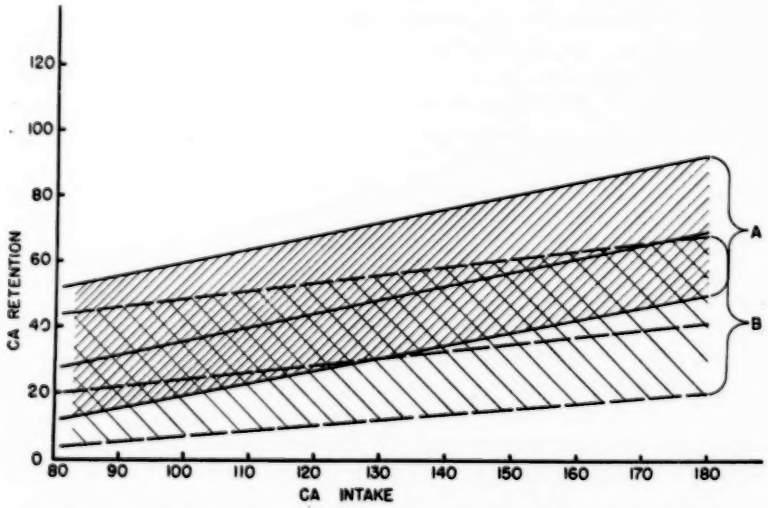

Fig. 4.—Range of retention values for varied intake of calcium in the infants whose growth curves are illustrated in Fig. 3 (shown in zone *B*), compared with retention zone in a series of normal infants under the same regimen.

intercurrent otitis. Retentions of phosphorus were similarly depressed.[12] It may be assumed that if impairment of the degree indicated were to occur continuously or frequently, eventually it would reflect itself not only in the quality but also in the quantity of skeletal tissues, and thus lead to stunting of growth.

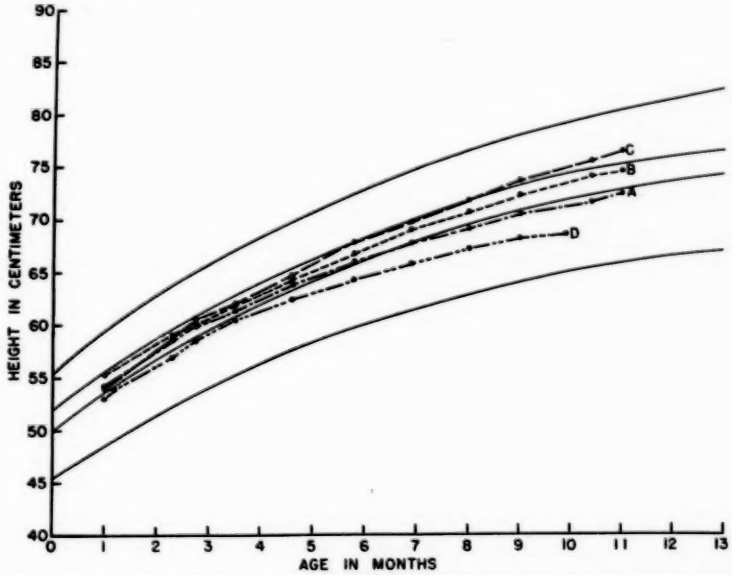

Fig. 5.—Average height curves for four groups of infants, superimposed on Kornfeld's range of average values for the first year of life. This chart illustrates the effect of varied levels of intake of vitamin D on average growth in height. Group *A* received no added vitamin D with the usual infant's diet; group *B* received 135 units daily; group *C* received 400 units daily; group *D* received 1,800 units or more daily. Note that growth is promoted by levels up to 400 units, and apparently inhibited in some measure by the large doses frequently prescribed for the normal infant.

Minor variations in the regimen of infant feeding may exert favorable or unfavorable effects on the concurrent rate of growth. An example, observed in the course of metabolic studies conducted by this department, is illustrated in Fig. 5. In a study of the retentions of calcium and of phosphorus in infants whose diets were equivalent aside from the amount of vitamin D which each received, it was found that there was an unquestionable relationship between the rate of growth of the infants and the amount of vitamin D which each was receiving. Curve *A*, Fig. 5, is based on a study reported by Baldwin in 1920; it represents the growth of a group of Iowa infants whose diets included no added vitamin D. Curve *B*, just above this, corresponds to the growth of the group of infants receiving milk containing 135 units of vitamin D to the quart. The uppermost curve, *C*, is that of the infants receiving 400 units of vitamin D daily. However, here the linear relationship breaks; the growth of those receiving 1,800 units or more daily is consistently

lower than any of the other groups, as expressed by the lowermost curve, *D*.[13] Interpreting this clinically, it means that, whereas the infant who receives the amount of vitamin D (135 units) contained in irradiated milk avoids rickets and also grows better than the child who receives no vitamin D, the child who receives 400 units daily may do still better, as evidenced by his rate of growth and his level of retentions of calcium. However, the infants who received as much as 1,800 units of vitamin D daily (about the amount contained in three teaspoonfuls of good grade cod-liver oil) showed definite suppression of growth.

SUMMARY AND CONCLUSIONS

In view of the foregoing discussion, what is the significance of a child's height and weight at any moment? Broadly speaking, it may be said to reflect the child's propensities as they have been molded by his conditions of living. It must be recognized that rates and degrees of ultimate growth show individual peculiarities, and that hard and fast rules cannot be set up as guides for any person.

It seems logical to assume that each person at birth carries with him into the world his own maximum capacity for growth and development in all regards, his limits having been determined by his genetic characteristics and by other conditions operative prior to his birth. It may be inferred that he cannot surpass these maximum values under any ordinary circumstances. What is the likelihood that he will attain them? This will be determined through the nature of factors which may serve as impediments in his development. To achieve maximum capabilities in all lines of development is beyond reason; to attempt maximum attainment in certain lines may bring the penalty of retardation along others. Optimum development evades definition; it probably will be different in nature and degree in various persons, and in different conditions of living. In general, the physician's view would favor the development of a symmetrical organism, well adapted in all phases for meeting its environment, rather than to strive for maximal development of body or of intellect. Nevertheless, the physician should not lose sight of the controllability of certain phases of development and the role he can serve in directing his patient toward a desirable pattern of growth.

Leaving the realm of philosophy and returning to the specific interests of the physician, the following recommendations are made: In each physical examination of the infant or child, include records of certain specific measurements and data regarding the rate and degree of growth and development. Appraise these against available standards of normality. Do not assume with finality that the child who falls within these standards is developing as well as he may be able to do under improved circumstances. When the infant or child falls below such standards, do not explain away his status without assuring yourself that correctable abnormality of body or of manner of life is not

present. Finally, accept standards of growth and development for what they are—cross-sectional averages of children from diverse groups and of varied levels of health—rather than ideals of achievement.

The writer wishes to express his appreciation of the valuable counsel offered by Dr. H. V. Meredith in reviewing anthropometric data.

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LEVELS OF ASCORBIC ACID IN THE BLOOD PLASMA OF APPARENTLY HEALTHY CHILDREN

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IT IS now generally accepted that a single observation of a low level of ascorbic acid in the blood plasma is not necessarily indicative of low tissue storage of vitamin C. There is evidence that the ascorbic acid content of whole blood, and particularly of the white blood cell and platelet layers (Butler and Cushman[1]), may be a more accurate index of vitamin C deficiency. Although it is probable that low plasma levels of ascorbic acid which are maintained over a considerable period of time are associated with a low content of ascorbic acid in other tissues, the final conclusion awaits further study. Kajdi and associates[2] state: "When the plasma level lies between 0.5 and 0.16 mg. per cent, one may be sure that the stores are not optimal; but it is impossible to tell the extent to which they are depleted." In a different approach to the problem of vitamin C adequacy, Roberts and associates[3] have observed accelerated growth and development in a group of institutional children who received, in addition to the regular diet, a supplement of two or three bananas daily for a period of nine months. At the end of the period of observation, the children who had received the bananas had, as a group, higher average ascorbic acid levels than did the control group. Roberts infers that the increased vitamin C intake was responsible for the better physical development.

Recently we have had the opportunity to determine the levels of ascorbic acid in the plasma in a group of institutional children on five occasions over a period of ten months. We were impressed by the relatively large percentage of low values at each examination (Fig. 1), and particularly by the number of apparently healthy children who maintained low levels throughout the entire period of the study. So far as we have been able to ascertain, similar observations of low plasma levels of ascorbic acid over a prolonged period have not been reported.

DETAILS OF PERIOD OF OBSERVATION

The original test group (First Group, May 6, Fig. 1) consisted of sixty children who were inmates of an exceptionally well-conducted orphanage. Determinations of plasma ascorbic acid constituted one of a number of tests and observations which were made in an attempt to learn whether there were factors other than tuberculous allergy which might

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*Dr. Cullen died a few weeks before the completion of this study.

influence the skin reaction to tuberculin.[4] This test group consisted of thirty children who reacted to very small amounts of tuberculin, and thirty children who failed to react to very large amounts. There were no differences in the distribution of plasma levels between these two subgroups. In view of the number of low levels observed, however, further determinations were made.

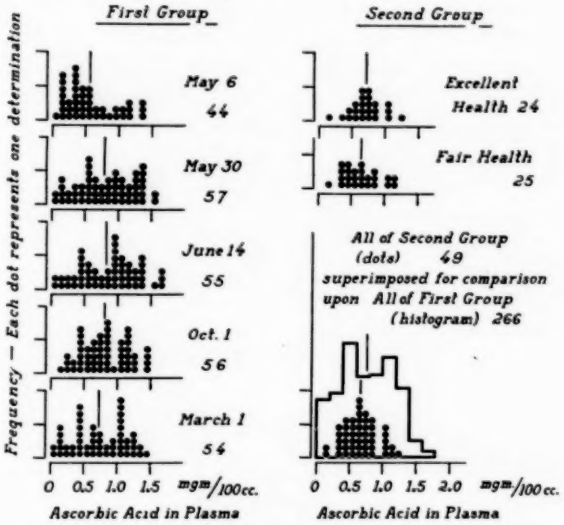

Fig. 1.—Levels of ascorbic acid in the plasmas of children in the orphanage. (Means are represented by vertical lines.)

During the period of observation, nine of the children were dismissed from the institution, but nine other children were added to the series, their selection being based on their reaction to tuberculin. Thus, sixty-nine different children were included in the First Group, and each child had from one to five determinations of ascorbic acid in plasma during the ten-month period. A number of determinations were excluded because of hemolysis of the blood sample and one determination was excluded because the child had an acute infection of the upper respiratory tract at the time of observation. Of the entire group, thirty-four children were represented in all five determinations, ten children in four, eight in three, fifteen in two, and two in one each.

To avoid changes in their usual intake of vitamin C, efforts were made to prevent the children from knowing the purpose of the blood examinations, and the dietician presumably did not know that the study was in progress. The children ate in a large dining room and all of them had access to the same diet. Additional servings were permitted as desired. The available ascorbic acid in the daily diet for a period of four consecutive weeks, estimated on the basis of average servings, ranged from

21 to 122 mg., with an average of 60 mg. Dietary histories obtained directly from the children did not reveal variations in eating habits which would explain the respective plasma levels of ascorbic acid.

Physical examination of ten of the eleven children who consistently had plasma levels of ascorbic acid below 0.5 mg. per cent revealed no gross abnormalities, and their nutritional status was approximately average. For example, their combined weight was 1,054 pounds, with an expectancy for height and age of 1,061 pounds. With the exception of two children who were, respectively, of the moderately obese and the tall thin types, there were no gross individual variations. The gums of all these children were uniformly healthy, and there was no difference in the incidence of dental caries* between the children with high and the children with low plasma levels of ascorbic acid. According to the records maintained by the two resident physicians of the institution, none of the children with low plasma levels was rated as having frequent infections. Blood hemoglobin and complement determinations† were obtained on the children of the First Group. The hemoglobin values ranged from 12 to 15.8 Gm. per cent, with no correlation between hemoglobin and ascorbic acid values. The blood complement values were all within the normal range.

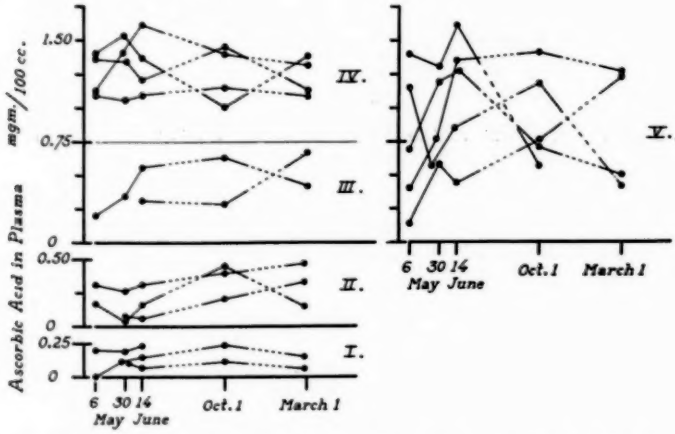

Fig. 2.—Representative "curves" of the plasma levels of children in the First Group.

Because of the possibility that the sixty-nine children of the First Group might not be representative of the entire institution, and because we wished to obtain additional evidence regarding the relation between plasma levels of ascorbic acid and the nutritional status or the state of health, a second group of forty-nine children was selected for study.

*We are indebted to Dr. John Schueller for data regarding dental caries.

†Complement determinations were made by Dr. P. Wasserman of the May Institute for Medical Research, Jewish Hospital, Cincinnati.

This included twenty-four children who were rated high in health and physical development and twenty-five who were considered to be slightly below average (Second Group, Fig. 1). Children who had chronic infections sufficient to require hospitalization were not included.

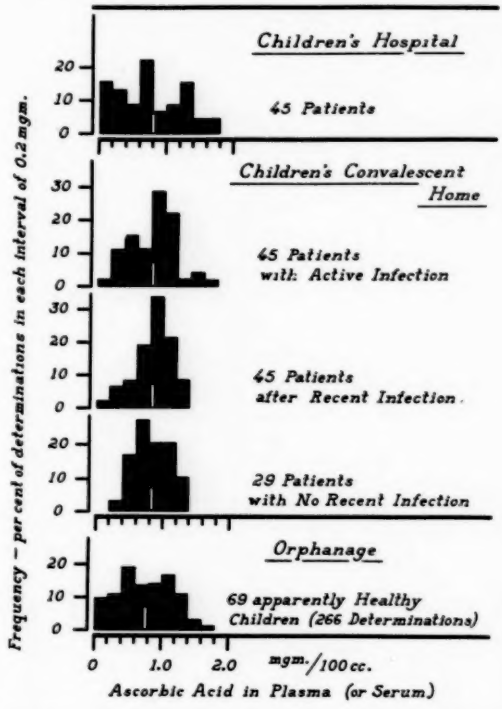

Fig. 3.—Comparison of apparently well children of the orphanage with those in the hospital and in the convalescent home. (Means are represented by vertical white lines.)

In view of the number of low plasma levels of ascorbic acid among the apparently well children in the orphanage and the previously observed association of low plasma levels with infection, data obtained from children in a convalescent home and from children in an "active" ward in the Children's Hospital are shown for comparison (Fig. 3).[5] The cases from the Children's Hospital included both infectious and metabolic diseases, although cases of clinical scurvy were excluded. There was no selection of cases at the convalescent home, the data presented being obtained in a survey of vitamin C nutrition in that institution and divided into the three subgroups shown after the survey was completed. The estimated amount of vitamin C available daily in the diets of the Children's Hospital and the convalescent home were 130 and 120 mg., respectively.

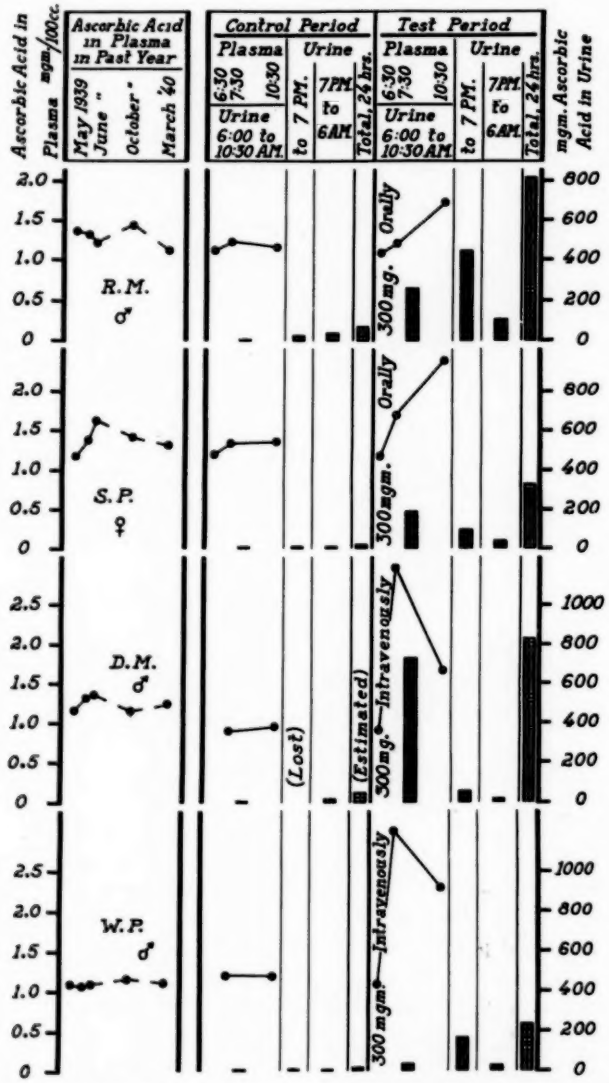

Fig. 4.—Response of children with high plasma levels of ascorbic acid to a single dose of 300 mg. of ascorbic acid. (Plasma levels are shown by dots connected by lines. The entire amount of ascorbic acid excreted in a designated interval is represented by a solid vertical bar. The total amount for each twenty-four-hour period is shown by a latticed vertical bar.)

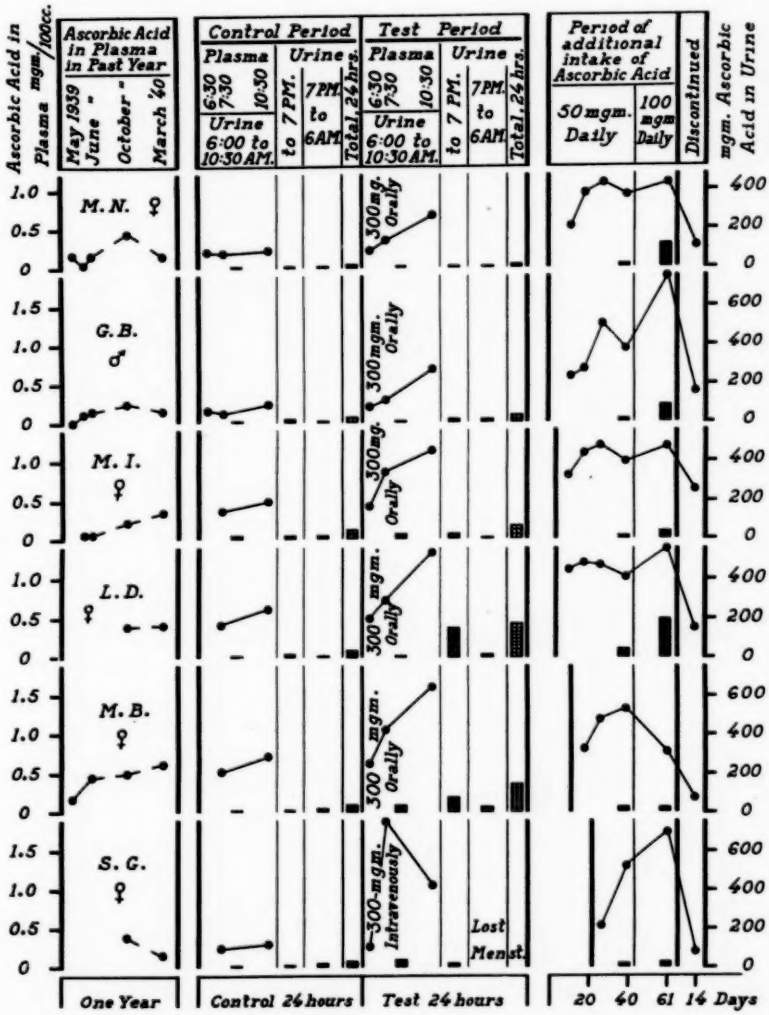

Fig. 5.—Response of children with low plasma levels of ascorbic acid to a single dose of 300 mg. and to subsequent daily ingestion of 50 and of 100 mg. of ascorbic acid. (The symbols are the same as those in Fig. 4 except that a vertical bar in the "period of additional intake" designates the amount of ascorbic acid in an overnight specimen of urine taken at the time of the plasma specimen represented by the dot above it. The "period of additional intake" followed immediately after the "test period" in *all* cases.)

The response to the administration of large amounts of ascorbic acid,* a so-called "saturation test," was observed in seventeen of the children in the orphanage. Thirteen of them had low levels of ascorbic acid in the plasma, and four had high levels. In each instance the twenty-four-hour test period was preceded by a twenty-four-hour control period. The children were kept in the hospital of the orphanage during this time. The twenty-four-hour control period was started at 6 A.M., the child voiding at this time and the specimen being discarded. The urine was collected in three samples, the first containing that voided from 6 A.M. to 10:30 A.M.; the second, from 10:30 A.M. to 7 P.M.; and the third from 7 P.M. to 6 A.M. Five grams of metaphosphoric acid (20 c.c. of 25 per cent solution) were placed in the bottle prepared for the initial sample. After collection, the urine was diluted to 200 c.c. Similarly, 12.5 Gm. were added to each of the bottles for the second and third portions of the urine, which were each subsequently diluted to 500 c.c. Determinations of plasma ascorbic acid were made on blood obtained at 6:30, 7:30, and 10:30 A.M., respectively. During the following day, the "test period," urine and blood specimens were obtained in an identical manner, and 300 mg. of ascorbic acid were administered, either orally or intravenously, immediately after the collection of the 6:30 A.M. blood specimen (Figs. 4 and 5).

Some of the children with persistently low plasma levels were then fed ascorbic acid in addition to that contained in their regular diet. They received 50 mg. per day for periods of time varying from seventeen to thirty-eight days and then 100 mg. per day for twenty-one additional days (Fig. 5).

METHODS OF ANALYSIS

For the determination of ascorbic acid in plasma, the blood was drawn from a vein into a dry syringe, transferred to a centrifuge tube containing heparin, and centrifuged for ten minutes within, at most, one-half hour after its withdrawal. The plasma was pipetted directly from above the layer of cells, and 0.5 c.c. was transferred to a centrifuge tube. To this, 0.5 c.c. of water and 1.0 c.c. of 5 per cent solution of metaphosphoric acid were added and immediately mixed with a stirring rod. This mixture was then centrifuged for ten minutes, after which approximately 1 c.c. of the supernatant clear liquid was drawn into a graduated pipette and 0.4 c.c. delivered to each of two depressions in a spot plate. These two samples, each with its blank of 0.4 c.c. of 2.5 per cent metaphosphoric acid, were titrated with 2-6 dichlorophenolindophenol solution equivalent to from about 0.02 to 0.04 mg. ascorbic acid per 1 cubic centimeter of dye. The accuracy of this procedure was established and maintained by occasional standardization of the stock of dry ascorbic acid against iodine and regular standardization of the dye against fresh solutions of the ascorbic acid; by comparison of the microtitration method with macrotitration, and also with the method of Bessey,[6] using the Evelyn electric colorimeter; by occasional tests of the loss of ascorbic acid in whole blood, plasma, and protein-free solution; and by adequate precautions to exclude traces of copper, chromic acid, or other oxidizing or reducing substances.

*The ascorbic acid used in this study was furnished by the courtesy of Hoffmann-La Roche, Inc.

For the determination of ascorbic acid in urine, the sample was first diluted, as mentioned before, to a concentration of 2.5 per cent of metaphosphoric acid, and then it was further diluted with 2.5 per cent acid in varying proportions, depending upon the concentration of ascorbic acid and upon the amount of pigment in the urine. Centrifugation was rarely required. The diluted urine was titrated directly, in the same manner as was the protein-free solution from plasma. The higher values are the more accurate because of the relatively smaller proportion of other reducing substances and the more diluted pigment. However, all values for urine are sufficiently accurate to leave no doubt regarding the conspicuous differences seen in the data and to support the inferences drawn therefrom.

DISCUSSION OF OBSERVATIONS

The distribution of the plasma levels of ascorbic acid in both the First and Second Groups of children of the orphanage is graphically illustrated by means of diagrams in Fig. 1. Each dot represents a single determination (duplicate titrations) on the plasma of a single subject. The most significant observation was the relatively large number of children with low plasma levels in all determinations. While there were both a greater number and a higher percentage of children with plasma levels below 0.5 mg. per cent in the first determination (May 6), there was a significant number (thirteen to nineteen children) with values within this range in the remaining four examinations. A substantial number of the children had markedly consistent plasma levels in all determinations made (Fig. 2). There were four children with levels below 0.25 mg. per cent in all determinations made on the plasmas (Division *I*, Fig. 2); eleven below 0.50 mg. per cent (*II*); twenty-one below 0.75 mg. per cent (*III*); sixteen above 0.75 mg. per cent (*IV*); and thirty-two who had levels both above and below 0.75 mg. per cent (*V*). As stated previously, no factors were found by physical examination or by a study of the hemoglobin content of their blood to distinguish those children with low plasma levels from those with high levels. This statement does not imply that there were not physical differences, but simply that, if there were any, they were not detected. There was no evidence in the plasma levels observed of seasonal variation dependent upon changes in dietary intake of vitamin C; on the contrary, the evidence presented indicates that sufficient vitamin C was available in the institutional diet for a significant number of children to maintain high levels of ascorbic acid in the plasma. In dividing these data into subgroups, we realize the danger of drawing the inference that those subjects who showed marked consistency within narrow ranges would not have shown greater variation in the levels of ascorbic acid in their plasmas if more frequent determinations had been made. It seems probable, however, that the levels of ascorbic acid are fairly well stabilized in those children who show such consistency at either high or low levels (Figs. 2, 4, and 5).

The occurrence of low levels of ascorbic acid in the plasmas of children with acute or chronic infections has been noted frequently. For

this reason it is of interest to compare the plasma levels in the apparently healthy children of the orphanage with the plasma levels of sick children in a hospital, and also with those of children who had subacute or chronic infections or who were in the convalescent stage. Fig. 3 shows the striking similarity between the plasma levels of the presumably well children of the orphanage and those of children in the other institutions. Even the group in the Children's Hospital contained only a slightly greater proportion of very low levels, and the mean was the same as that of the group in the orphanage. Subsequently, no correlation was observed when an attempt was made to determine whether selection of children in the orphanage on the basis of status of health would be reflected in comparable differences in the levels of ascorbic acid in the plasmas (Second Group, Fig. 1). While it is true that the twenty-five children rated as below average included nine having plasma levels below 0.5 mg. per cent, in contrast to only four below this level in the twenty-four rated as having excellent health, this difference is not significant. (P is between 0.2 and 0.1.*) From these observations it is clear that plasma levels of ascorbic acid cannot be predicted with accuracy from the physical appraisal.

Examples are shown in Fig. 4 of the response of the levels of ascorbic acid in the plasmas of children with existing high levels to a single large oral or intravenous dose of ascorbic acid (300 mg.), and in Fig. 5 of the effect on the plasma levels in children with low levels both of this single large dose and then of continued daily feeding of 50 mg. and then of 100 mg. of ascorbic acid in excess of that available in their regular diet. It will be seen that, while in children both with high and with low plasma levels of ascorbic acid the level was raised still higher, the urinary excretion was markedly greater in the children with high levels. In fact, for some unexplained reason, in two of the four cases illustrated, the urine contained reducing substances greatly in excess of the ascorbic acid administered. The markedly low urinary excretion of ascorbic acid after the test dose of 300 mg. in the children having lower plasma levels is perhaps the strongest evidence presented that these children not only had low plasma values throughout the period of study but that their tissue storage of vitamin C was below that which they were capable of attaining. That these children had the inherent capacity to store greater quantities of ascorbic acid and to maintain higher plasma levels of ascorbic acid is shown by the effect of continued feeding of from 50 to 100 mg. of ascorbic acid daily for periods of from twenty to sixty days (Fig. 5). The lower level in the plasma of M. B. (Fig. 5) after increasing the dose of ascorbic acid from 50 to 100 mg. daily is unexplained.

*P is the probability, calculated as a percentage, that a difference as large as or larger than that observed would arise by chance alone.

SUMMARY

Levels of ascorbic acid in the blood plasma which are ordinarily associated with vitamin C deficiency have been observed in a large proportion of apparently healthy children. In some instances, the low plasma levels persisted for a period of ten months, without apparent ill effect on the health of the children. This observation, of course, is not proof that such plasma levels are desirable, nor that they have not or will not eventually account for nutritional disturbances.

It appears that, although single determinations of ascorbic acid levels in the plasma do not reveal the state of vitamin C storage within the body, repeated determinations over a period of time may offer a more accurate measure of such storage.

No conclusion is drawn concerning the *minimal* adequate level of ascorbic acid in the plasma. However, if this level is to be considered as 0.6 mg. per cent, or even 0.4 mg. per cent as suggested by Ralli,[7] then it is obvious that dietary standards should be revised. Particularly should this be the case in planning institutional diets where there is less opportunity for observation of the individual child's intake.

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VITAMIN E IN THE TREATMENT OF MUSCLE DISORDERS OF INFANCY AND CHILDHOOD

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THE first observation on the need of vitamin E for normal muscle metabolism was made by Evans and Burr,[1] in 1928, when they permitted rats low in vitamin E to suckle and rear their young. Toward the end of the lactation period, they noticed that the majority of the apparently healthy young rats developed a mysterious malady, of which the main characteristic was a muscular paralysis and inability to right themselves when placed on their backs. One-third of the affected animals died, a small group recovered without sequelae, and about one-half continued to exhibit some evidence of paralysis even after recovery. The recovered animals usually belonged to the group most mildly affected. Infection and lack of other vitamins were eliminated as the cause of this paralysis. Feeding vitamin E to the mother prevented the disease; also the administration directly to the young was just as effective. Morelle[2] was able to substantiate the findings of Evans and Burr and also noted that if wheat germ oil was administered to the mother ten days before the litter was born or as late as two weeks after birth, no paralysis developed.

In 1931 Goettsch and Pappenheimer reported the production of muscular dystrophy in guinea pigs and rabbits[3] on a vitamin E deficient diet, a similar myopathy in ducklings,[4] and involvement of smooth muscle of the gizzard in young turkeys on the same diet.[5]

In 1936, the same authors[6] also succeeded in transmitting muscular dystrophy to rabbits in utero, in an instance in which a female rabbit which developed muscular dystrophy on a diet low in vitamin E survived and was able to complete gestation and give birth to living young. The young died shortly after birth, and microscopic examination of their musculature showed lesions identical with those found in certain stages of adult nutritional muscular dystrophy, indicating that in some instances the dystrophy is already developed before birth. That this nutritional type of paralysis is not confined to suckling young rats of vitamin E deficient mothers was proved by Ringsted[7] in 1935, when he produced paresis of the hindquarters, later associated with symmetrical denuding and hypoesthesia of the hind legs and tail, in rats from normal

From the Neurological Service of the Elliot Hospital and the Crippled Children's Services of the State of New Hampshire.

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Eli Lilly and Co. have supplied the wheat germ oil used in this study.

mothers deprived of vitamin E from weaning. Burr, Brown, and Moseley[8] also observed a similar paralysis in older rats on a diet deficient only in vitamin E. That the symptoms in the older animals may be due also to nervous system involvement has been suggested by Lipshutz[9] and Einarson and Ringsted.[10] The latter after having found changes in the lateral and posterior columns of the spinal cords in their animals, decided that the cord lesions "resemble closely a combination of the two most important degenerations occurring in man, namely, tabes dorsalis and spinal progressive muscular atrophy."

Microscopic study of the involved musculature was carried out by Olcott,[11] Pappenheimer,[12] and Telford, Emerson, and Evans.[13] They all agree in their findings, and I shall quote from the description of the latter authors.

"The first stage of degeneration can often be demonstrated before the animal shows any obvious signs of paralysis. The lesion manifests itself as a waxy, hyaline or Zenker's degeneration of the individual muscle fibers. In the necrosis of the fiber the contractile substance breaks up into swollen, homogeneous, hyaline segments. These masses may obtain a diameter double that of a normal fiber. The swollen segments (1) lose their hyalinization and become granular, (2) become reduced in size, and (3) finally become debris in the intersarcolemmic space. The muscle nuclei also undergo change. They are crowded against the sarcolemma of the swollen fiber segment and are pyknotic as the degeneration progresses and an increased number of fibers become affected."

This picture appears very similar to the changes described by Aring and Cobb[14] in dystrophic human musculature. Speaking of human beings, they say:

"The muscle fibers are of different shapes and sizes. In longitudinal section long fibers are seen to break in two or three segments, each of which may be surrounded by numbers of sarcolemma nuclei; increase in number of nuclei of muscle fibers is characteristic. Hyaline degeneration and vacuolation of the hypertrophied muscle fibers are common; in the neighborhood of tendinous attachments the hypertrophied fibers become fibrous. As the disease progresses muscle tissue is replaced by connective tissue and fat until one sees in a microscopic field only a few scattered fibers, some larger than normal, others atrophic."

CLINICAL APPLICATION

Although no definite disease conditions have been associated in the past with an insufficient amount of vitamin E in the diet, the similarity of the symptoms described in the animal dystrophic groups as compared with the findings in human beings has prompted the investigation of the value of vitamin E in the treatment of muscular dystrophies and related conditions in children and adults. The assumption that vitamin E was not specific for muscular dystrophies and that the action was also as that of a stimulant to muscle metabolism, especially in the young, prompted also its use in a number of other conditions where disturbance of muscle function was one of the prominent symptoms. In a previous paper,[15] I reported the beneficial use of wheat germ oil in muscular

dystrophies and in a case of subacute poliomyelitis and polyneuritis. Similar results were also obtained by Bicknell[16] who used wheat germ instead of wheat germ oil in cases of muscular dystrophy and myatonia congenita.

Of the four cases presented in this report, two are cases of pseudohypertrophic muscular dystrophy and two of myatonia congenita. The first case has been reported previously. He is a boy of 9 years, with no family history of this disorder. The mother had very little of green vegetables during her pregnancy and for about eight months after delivery while she was nursing the child. Symptoms were noted at the age of about 1 year. At the age of 8, he had a fairly advanced condition of pseudohypertrophic muscular dystrophy. After six months of treatment with wheat germ oil and vitamin B complex, the dystrophic musculature was replaced by normal tissue, and except for some lordosis, he has no residual signs.

The second boy of 8 years comes from a dystrophic family. Two maternal cousins have muscular dystrophy, and an older half-brother is badly crippled from this disorder. The mother had been married twice and she is the carrier in the family. This boy's condition was advanced on admission and he has been under treatment for three months. Since he began treatment, the muscles of his legs have lost their rubbery consistency, he is able to get around better, and he has developed new muscle tissue in his arms, forearms, and thighs. He is stronger, has gained 6 pounds in weight under vitamin E and B therapy, but is still unable to get up from a sitting position without assistance.

The next two patients suffer from myatonia congenita. The boy of 7 has shown myatonic and myasthenic symptoms since birth. He was unable to raise his head till he was 4 years old, and since then, only with difficulty; he also was unable to keep his eyelids open for any length of time, his voice was weak, and he weighed only 29 pounds on admission three months ago. He had no palpable musculature when first seen. Now he is able to sit up all day, takes a number of steps without assistance (he is handicapped because of contractures), and has developed new musculature in his extremities.

The fourth patient is a girl of 8 years. One older sister is also afflicted with the same disorder. On admission she had difficulty in changing position while lying in bed, was rather helpless, and was unable to feed or dress herself. She had no palpable muscle tissue and showed generalized areflexia. Since she was placed on vitamin E, some muscle tissue has appeared in her biceps and triceps, she is able to sit up most of the day, and also is able to walk in braces, with no assistance.

Although these patients have not recovered entirely, except the first one, the formation of new muscle tissue and the generalized increase in strength and sense of well-being has been very striking and has only become apparent since they have been placed on vitamin E.

Also, through the facilities of our crippled children's and orthopedic clinics, with the cooperation of Dr. Ezra A. Jones and Dr. Carl R. Friborg, we have had an opportunity to observe a large group of children between the ages of 1 and 5 years who are brought in to the clinic because of poor muscular development, inability to hold up their heads until they are 2 or 3 years old, and retardation in beginning to stand alone or walk. Some of these children were premature at birth and remained of small stature and considerably underweight. Another group is represented by the apparently well-nourished or even obese infant with a great deal of subcutaneous fat but very poorly developed musculature. Treatment in the past consisted of orthopedic manipulation, massage, attention to pronated feet, and occasional dietary suggestions. The neurologic examination usually is negative, except in cases associated with spastic diplegia or other forms of natal or prenatal injuries.

The possibility that the muscle disturbances observed in this group of children were caused by vitamin E deficiency in a lesser degree than present in the muscular dystrophies and myatonias has prompted the investigation of the addition of vitamin B complex and vitamin E to the children's diet. While the addition of vitamin B complex tended to improve their appetite or produced increase in weight, the response in muscle strength was rather slow. When vitamin E in the form of wheat germ oil was also added to the vitamin B complex, the response in rate of improvement in muscle strength was more rapid in appearance. Usually within a month the mother reported that the child was able to stand better, hold up its head, which it could not do formerly, turn over without assistance, and also make attempts at walking alone, which it did not do before. An increase in mental alertness also was observed in some cases at the same time. Usually the children with the flaccid musculature responded much better than the spastic group.

The dosage in the dystrophic and myatonic group is 2 to 4 c.c. of fresh wheat germ oil given daily, together with the vitamin B complex. In the infants and young children with the generalized muscular hypotonia, the initial dose is 8 to 12 minims of wheat germ oil, preferably with B complex. The mixture is usually well tolerated by infants and children. On rare occasions a papulomacular reddish skin rash has appeared in patients under treatment, which is probably due to some other ingredients in the oil. The rash disappears rapidly after the medication is temporarily discontinued.

DISCUSSION

The exact part played by vitamin E in the human dietary still remains to be determined. From pathologic studies in E-deficient animals, certain conclusions, however, can be drawn. There is apparently a greater demand for it in the rapidly growing young organism. An adequate amount seems to be required for the maintenance of normal muscle

metabolism and muscle growth. The finding of pituitary and thyroid aplasia in rat offsprings of E-deficient mothers[17, 18] would suggest that vitamin E is required by the embryo for the synthesis of certain glands of internal secretion. After the study of degeneration in testes produced in E-deficient rats, Mason[19] concluded that vitamin E is especially needed by the cell nucleus at a period when rapid cell proliferation is taking place, which would include muscle tissue in the growing young. At a later age its deficiency in the diet was observed to result in diminished vigor and failure of growth,[20] while in older animals, sterility and nervous system disturbances were more apt to occur. All of the above findings would suggest that the protective influence of vitamin E is required especially during early periods of growth, although its absence from the diet will also produce neuromuscular damage in the older animals. The variety of changes ascribed to vitamin E deficiency would indicate that, like vitamin B complex, it is composed of many fractions, each with effective action in its own sphere.

As long as the newborn infant depends for its supply of vitamin E mainly on the reserves stored during its intrauterine existence and acquired through placental transmission,[21] it is plausible to assume that the anlage for such cases of muscle dystrophy has been laid down during pregnancy through dietary deficiency in the mother, for the supply of vitamin E received through maternal milk is limited and has apparently little protective value.[21] Added proof for this assumption is found in Pappenheimer and Goettsch's[6] observation of dystrophic changes in the musculature of newborn rabbits. That cow's milk is occasionally very low in vitamin E has been established by Vogt Möller,[22] who found fetal resorption in cows, which he attributed to the low vitamin E contents of their diet. Milk from such cows, of course, will have very little protective value, and infants on such a milk diet will receive very little vitamin E. The prematurely born infant especially will be apt to suffer because vitamin E deficiency in the mother is in itself an occasional cause of premature birth. Vitamin E deficiency would also be suspected as one of the factors in producing the slow gain seen occasionally in this group of children. As to powdered milk, its content of vitamin E is even less than that of fresh milk.[23]

The diet of the older child is also frequently just as deficient unless it contains cereals, lettuce, and green vegetables rich in vitamin E. This deficiency, all the year round and seasonal, in supposedly normal diets of adolescents has been pointed out by Bayer[24] and Shute.[25] Butter and other fats also lose their supply of vitamin E if they become rancid. Egg yolk, a rich animal source of supply, has been found to be deficient in this substance if not enough grain has been fed to the hens.

The actual amount of vitamin E required for normal tissue metabolism has not been fully established yet. It appears to be needed in larger quantities during infancy, adolescence, and pregnancy. There is a

possibility that it plays a part in forming a barrier against virus penetration in infancy.[26] Again there seem to be individual differences in the amount required for normal function and in the animal's ability to absorb and store vitamin E for future use. These variations would help to explain the divergence of symptoms of vitamin E deficiency observed in different species of animals. The extent of the deficiency, the age at which it occurs, and the lack of other vitamins may explain why, in certain animals, nervous symptoms predominate, while in others the brunt of the damage seems to be borne by the muscular system. Thus, extreme deprivation of vitamin E in the offspring through maternal inability to absorb or transmit vitamin E through the placenta to the fetus will result in myatonias. The improvement occasionally seen without treatment in such cases is possibly due to improvement in diet during infancy and childhood. Less severe intrauterine deficiencies will result in cases of pseudohypertrophic muscular dystrophy. Milder forms of deprivation will become apparent in the frequently seen states of muscular hypotonia, generally poorly developed musculature, retarded growth, and slowness in beginning to walk in cases where other causes have been ruled out. What part deprivation of other vitamins plays in modifying the neurologic or muscular changes is open only to speculation at present.

CONCLUSIONS

Vitamin E is important for normal muscle growth of infancy and childhood.

In some children with poor muscular development the etiology may be deficiency of vitamin E.

Deficiency in the mother during pregnancy or her inability to transmit vitamin E to the offspring is possibly a factor in the development of impaired musculature of the newborn infant. It is probable that certain types of muscular dystrophy, some myatonias (Oppenheim), and selected cases of poor muscular development in the young infant are expressions of the same deficiency. This hypothesis is supported by the fact that administration of vitamin E is of definite therapeutic value in such cases.

Most infantile diets are likely to be deficient in vitamin E. It is suggested that in certain obscure nervous and muscular disturbances of infancy and childhood, vitamin E deficiency should be investigated as one of the causes.

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VITAMIN K AND THE PRENATAL AND POSTNATAL PREVENTION OF HEMORRHAGIC DISEASE IN NEWBORN INFANTS

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A RELATIONSHIP exists between hemorrhagic disease of the newborn infant and the prothrombin level of the blood. Lack of prothrombin causes a bleeding tendency. This hypoprothrombinemia can be successfully treated by the administration of vitamin K.

The purpose of this study is to contribute more data on the administration of vitamin K and its substitutes for the prevention and treatment of hemorrhagic disease in the newborn infant.

METHOD

Several methods have been devised for the determination of the blood prothrombin level, but few are applicable to the study in newborn infants. As Kato pointed out, most methods require large quantities of venous blood, which becomes a technical problem in the infant.

There are two main types of tests: those requiring oxalated blood and those requiring fresh blood. They are represented by the Quick and by the Smith techniques, respectively. The Quick method is the older and requires the use of oxalated blood. In Bray's and Kelley's modification of this method, only 0.5 c.c. of blood taken from the heel or from a vein are required. Kato advocates the use of a microdetermination. This method is more adequate for infants. It requires only 10 c.mm. of capillary blood, but this has to be oxalated too.

Smith has developed a simple bedside test for prothrombin determinations; he uses 0.9 c.c. of blood and 0.1 c.c. of thromboplastin solution. This test is rapid, yet it requires venous blood.

In our test, we have combined the attributes of the Kato and Smith tests. It is like Kato's a microdetermination, and like Smith's a rapid bedside method, requiring unoxalated blood.

PROTHROMBIN TEST

Fresh ox lung is obtained from a packing house and immediately brought to the laboratory. To each 15 Gm. of macerated lung tissues, 10 c.c. of 0.9 per cent solution of sodium chloride is added. This is placed in a mechanical mixer and extracted for from three to four hours. Then the mixture is filtered through heavy grade filter paper and is packed in ampoules each containing 0.5 c.c. Each ampoule is sealed and kept at freezing temperature. The thromboplastin must be kept

From the Parkland Hospital and the Pediatric Department of Baylor University College of Medicine, Dallas.

frozen until it is to be used. For each series of tests a fresh ampoule is used, and the thromboplastin is checked on normal adult blood. Such a solution should cause normal adult blood to begin clotting within twenty-two seconds (with a variation of ± two seconds).

We use a small pipette graduated to a 10-c.mm. mark. A stop watch is used for marking the time, and the test is easily done in a hollow ground-glass slide.

Technique.—Place 10 c.mm. of thromboplastin mixture in a hollow slide. From a heel or finger puncture, quickly draw 10 c.mm. of blood and rapidly transfer this to the drop of thromboplastin. Start timing as soon as the blood has been added. Dip a needle into the mixture every two seconds until the first strand of fibrin is observed. Note the time to this point. The test is done at room temperature of about 70° F.

In our series of tests, prothrombin times were determined on a group of normal adults each day and the prothrombin levels of the infants were reported in percentage of the adult normal, according to the calculation of Smith:

$$\frac{\text{Clotting time of normal adults in seconds}}{\text{Clotting time of infants in seconds}} \times 100 = \text{Infant prothrombin level in percentage of adult normal}$$

RESULTS

Our investigations were done on seventy infants who were full-term infants and were physically well developed at birth. They were studied for the first six days of life. Tests were made on the first, second, fourth, and sixth days after birth. The tests in all cases were run in duplicate.

Group I was composed of thirty normal newborn infants. One hundred and seventy-eight individual tests were made which showed that the average prothrombin time on the day of birth was 58.3 per cent that of normal adult blood. By the fourth day it dropped to 55.4 per cent, and on the sixth day it returned to 57.1 per cent. All thirty babies in this group were given only water during the first hours, and then were placed on regular breast feedings.

Group II was also composed of thirty full-term newborn infants. To these vitamin K concentrate (2 methyl-1.4 naphthoquinone)* was administered in order to determine its effect upon the normal prothrombin time. Each baby was given 1 mg. of vitamin K concentrate at 8 A.M. and at 6 P.M. for the first six days of life. The vitamin K concentrate was dissolved in water. Vomiting occurred in no case. The first prothrombin determination was made as soon after birth as possible and before the first dose of vitamin K was given.

It was seen that the average prothrombin time for this group of babies on the first day of life was 59 per cent, which is, as in the first

*The vitamin K concentrate used in this study (Proklot) was kindly supplied by Eli Lilly and Co.

group of babies studied, a low initial level. On the second day of life the average was 71 per cent, and by the fourth day of life the babies in this group obtained an average level of 81 per cent. This prothrombin level continued to increase, reaching an average level of 85 per cent by the sixth day of life.

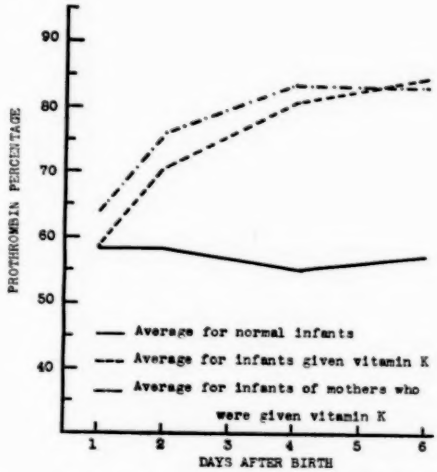

Fig. 1.—General average for all infants, showing the normal prothrombin percentage and the effect of the use of vitamin K.

In Group III of our study we have attempted to show the effect of administration of vitamin K to the mothers upon the prothrombin level in the infants. It was a study of ten babies to whose mothers 2 mg. of vitamin K concentrate with adequate bile salts* were given on admission to the hospital. This dose was repeated after six hours, so that the mothers received 4 mg. of the concentrate before delivery. The administration of vitamin K with bile salts to the mother was continued after delivery twice daily for six days. Prothrombin determinations were made daily on these babies. They showed that on the first day of life the average prothrombin time was 64 per cent and that by the second day it had increased to 76 per cent. There was a further rise of the level to 80 per cent on the fourth day, where the level remained through the sixth day.

SUMMARY

A rapid microtest for prothrombin determinations, especially in newborn infants, which requires only 10 c.mm. of capillary blood is described.

This method was applied in a study of seventy normal infants. A total of 476 determinations was made.

*Bilron, Lilly.

In a study of thirty normal infants it was found that the average prothrombin time on the first day of life was 58.3 per cent according to Smith's calculation, lowering to 54.4 per cent on the fourth day, and then increasing to 57.1 per cent of adult normal by the sixth day. This is confirmative of a physiologic hypoprothrombinemia in normal newborn infants.

The prothrombin level of another group of thirty normal newborn infants to whom vitamin K concentrate was administered for the first six days of life rose from 59 per cent average to 70.9 per cent by the second day, to 80.9 per cent by the fourth day, and to 84.4 per cent of adult normal by the sixth day of life.

After the administration of vitamin K to ten mothers while in labor and during the first six days after delivery, the prothrombin level of their babies rose from 63.3 per cent on the first day to 75.3 per cent on the second day, to 83 per cent of adult normal on the fourth day, and remained on this level for the following two days.

Studies such as ours indicate the great importance of determining the prothrombin time in the newborn infant for the detection of clinical or subclinical "hypoprothrombinemia hemorrhagica neonatorum." They show that the administration of vitamin K raises the prothrombin level in the newborn infant and maintains the prothrombin at a safe level.

For the prevention of hemorrhagic disease in newborn children, vitamin K concentrates can be given, with the same effect, directly to the infant or to the mother before and after delivery.

We wish to express our appreciation to Dr. J. W. Lanius and to Dr. J. S. Montgomery for their cooperation in this study.

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2519 OAK LAWN AVENUE

VITAMIN P AND CAPILLARY FRAGILITY

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SZENT-GYÖRGYI[1] and his collaborators in 1936 reported the existence of a new substance governing vascular permeability. They "found that in certain pathological conditions, characterized by an increased permeability or fragility of the capillary wall, ascorbic acid was ineffective while the condition was readily cured by the administration of extracts of Hungarian red pepper (vitaprie) or lemon juice." Subsequently, fractionization of these extracts revealed that the active principle present in a fraction consisted of pure flavone or flavonol glucoside.[2] The mixture of these flavones was termed "citrin," and because the action of this substance more nearly resembled that of a vitamin than of a pharmaceutical preparation, the name vitamin P was suggested.

Investigation with guinea pigs was used to show that the time of survival of males on a scorbutic diet was prolonged by supplements of vitamin P given orally and prepared from lemon juice. On autopsy, these animals who had received vitamin P showed fewer hemorrhages than the control group. However, Zilva,[3] and later Moll,[4] reported their inability to confirm the work with guinea pigs. Szent-Györgyi[5] subsequently was unable to repeat his earlier experiments. Therefore, since investigation on guinea pigs has failed to demonstrate the presence of a substance necessary for the maintenance of normal capillary fragility, evidence for the existence of this vitamin P must rest on the original clinical observations and the successful reduplication of these results.

Numerous investigators—Greene[6] (1934), Perry[7] (1935), Abt and his co-workers[8] (1936), Scarborough and Stewart[9] (1938), Liebman and associates[10] (1938), Rapaport and co-workers[11] (1940)—during the past few years have been unable to correlate increased capillary fragility with states of vitamin C deficiency.

Scarborough and Stewart, in 1938, investigated capillary fragility in six cases of generalized vitamin deficiency and showed that the oral administration of hesperidin (vitamin P) could control the number of induced petechiae hemorrhages in such subjects. Scarborough[12] in 1939, working with human subjects, adduced additional evidence which established the existence of a factor which decreases capillary fragility.

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The vitamin P used in this study was supplied through the kindness of the California Fruit Growers Exchange, and was used as calcium eriodictate.

The present study was undertaken on a group of 100 ambulatory patients, all children attending the Pediatric Allergy Clinic. Of this group, forty-nine children were found to have abnormal capillary fragility, and fifty-one to have normal capillary fragility. In a further study of the forty-nine children found to have abnormal capillary fragility, twelve children were selected because repeated capillary tests were found to be consistently abnormal. These children were tested with a positive pressure test at periodic intervals for at least six months. Vitamin P was put in small capsules, each capsule containing 25 mg., and the children were told to take the designated amount in divided dosage daily. All capillary fragility tests were done following the Wright modification of the Rumpel-Leede test. We accepted Wright's

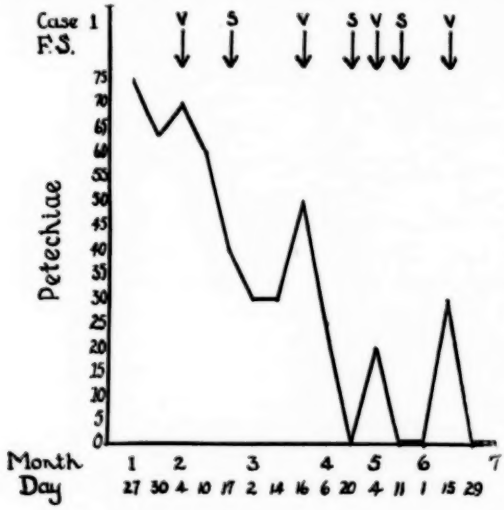

Fig. 1.—*V*, Vitamin P, 100 mg. daily; *S*, stop vitamin P.

CASE 1: F. S.

DATE	NUMBER OF PETECHIAE	
1/27/40	75	
1/30/40	66	
2/ 4/40	70	Started vitamin P, 100 mg. daily
2/10/40	60	Continued vitamin P
2/17/40	40	No vitamin P
3/ 2/40	30	No vitamin P
3/14/40	30	Started vitamin P, 100 mg. daily
3/16/40	50	Continued vitamin P
4/ 6/40	25	Continued vitamin P
4/20/40	10	No vitamin P
5/ 4/40	20	Started vitamin P
5/11/40	0	No vitamin P
6/ 1/40	0	No vitamin P
6/15/40	30	Started vitamin P, 100 mg. daily
6/29/40	0	No vitamin P

standard of ten or less petechiae as normal, from ten to twenty as borderline, and twenty or more as evidence of capillary fragility. Blood ascorbic acid determinations were done routinely on all of these children with elevated capillary fragility tests, and when the levels were found to be below normal, ascorbic acid in adequate dosage was given by mouth until normal levels of vitamin C in the blood stream were obtained.

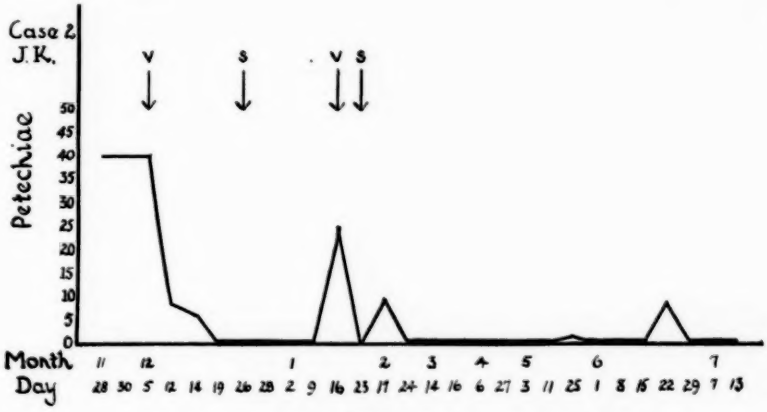

Fig. 2.—*V*, Vitamin P, 100 mg. daily; *S*, stop vitamin P.

CASE 2: J. K.

DATE	NUMBER OF PETECHIAE	
11/28/39	40	
11/30/39	40	
12/ 5/39	40	Started vitamin P, 100 mg. daily
12/12/39	8	Continued vitamin P
12/14/39	6	Continued vitamin P
12/19/39	0	Continued vitamin P
12/26/39	0	Stopped vitamin P
12/28/39	0	No vitamin P
1/ 2/40	0	No vitamin P
1/ 9/40	0	No vitamin P
1/16/40	25	Started vitamin P, 100 mg. daily
1/23/40	0	No vitamin P
2/17/40	10	No vitamin P
2/24/40	0	No vitamin P
3/14/40	0	No vitamin P
3/16/40	0	No vitamin P
4/ 6/40	0	No vitamin P
4/27/40	0	No vitamin P
5/ 3/40	0	No vitamin P
5/11/40	0	No vitamin P
5/25/40	2	No vitamin P
6/ 1/40	0	No vitamin P
6/ 8/40	0	No vitamin P
6/15/40	0	No vitamin P
6/22/40	8	No vitamin P
6/29/40	0	No vitamin P
7/ 7/40	0	No vitamin P
7/13/40	0	No vitamin P

Case 3: A. F.

DATE	NUMBER OF PETECHIAE	
11/28/39	50	
12/ 5/39	50	
12/12/39	50	Started vitamin P, 100 mg. daily
12/19/40	20	Continued vitamin P
12/26/39	50	150 mg. daily
1/ 2/40	50	Continued vitamin P, 150 mg. daily
1/ 9/40	0	Stopped vitamin P
1/16/40	25	Started vitamin P, 150 mg. daily
1/23/40	25	Continued vitamin P, 150 mg. daily
2/ 1/40	20	Continued vitamin P, 150 mg. daily
2/ 6/40	0	Continued vitamin P, 100 mg. daily
2/13/40	50	Continued vitamin P, 150 mg. daily
2/20/40	50	Continued vitamin P, 150 mg. daily
3/10/40	30	Continued vitamin P, 150 mg. daily
4/22/40	8	Continued vitamin P, 150 mg. daily
5/ 4/40	0	No vitamin P
5/18/40	0	No vitamin P
6/10/40	0	No vitamin P

Case 4: S. K.

11/30/39	40	
12/ 5/39	40	
12/28/39	40	Started vitamin P
2/ 1/40	30	No vitamin P
2/24/40	0	No vitamin P
4/ 6/40	15	No vitamin P
4/13/40	0	No vitamin P
4/20/40	10	No vitamin P
4/27/40	0	No vitamin P
5/ 4/40	0	No vitamin P
5/25/40	10	No vitamin P
6/ 7/40	0	No vitamin P
7/18/40	0	No vitamin P

Case 5: R. R.

1/27/40	60	
2/10/40	50	
2/17/40	45	
2/24/40	35	
3/14/40	55	Started vitamin P, 100 mg. daily
3/16/40	25	Continued vitamin P
3/23/40	35	Continued vitamin P
4/ 6/40	0	Stopped vitamin P
4/20/40	10	No vitamin P
4/27/40	0	No vitamin P
5/ 4/40	0	No vitamin P
5/11/40	0	No vitamin P
5/18/40	1	No vitamin P
6/ 1/40	20	No vitamin P
6/ 8/40	20	No vitamin P
6/15/40	20	No vitamin P
6/22/40	10	No vitamin P
6/29/40	20	No vitamin P
7/ 7/40	25	No vitamin P
7/13/40	25	Started vitamin P, 100 mg. daily
7/20/40	0	Stopped vitamin P

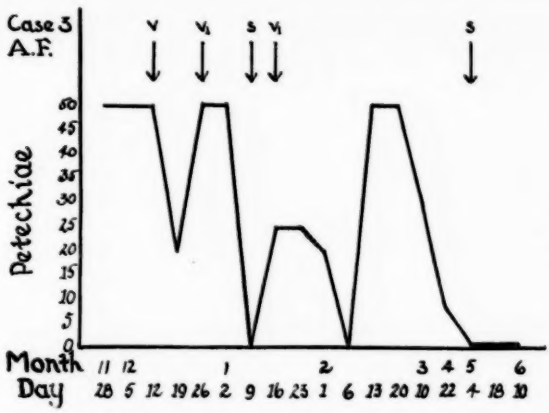

Fig. 3.—*V*, Vitamin P, 100 mg. daily; *V*$_1$, vitamin P, 150 mg. daily; *S*, stop vitamin P.

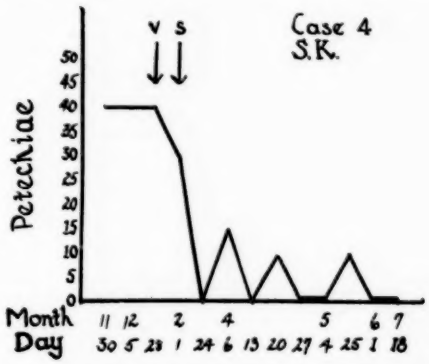

Fig. 4.—*V*, Vitamin P, 100 mg. daily; *S*, stop vitamin P.

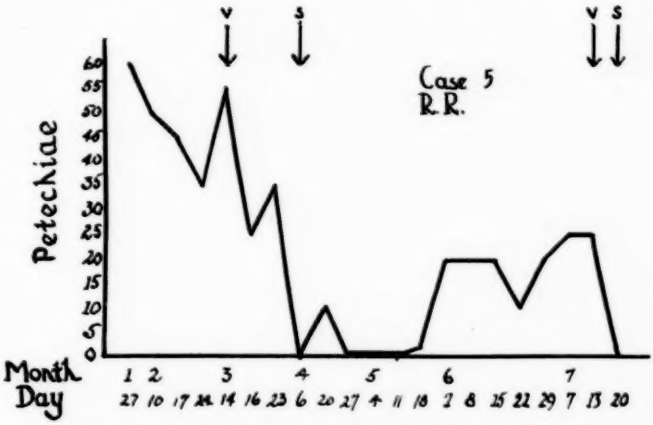

Fig. 5.—*V*, Vitamin P, 100 mg. daily; *S*, stop vitamin P.

CASE 6: W. L.

DATE	NUMBER OF PETECHIAE	
11/30/39	50	
12/ 5/40	50	
12/19/40	50	Started vitamin P, 100 mg. daily
12/26/40	50	Continued vitamin P
12/28/40	25	Stopped vitamin P
1/ 9/40	25	No vitamin P
1/11/40	25	No vitamin P
1/16/40	25	Started vitamin P
1/18/40	10	Continued vitamin P
1/23/40	25	Continued vitamin P
1/25/40	25	Continued vitamin P
1/27/40	30	Increased vitamin P to 150 mg. daily
2/ 6/40	0	Reduced vitamin P to 100 mg. daily
2/10/40	10	Continued vitamin P
2/13/40	10	Continued vitamin P
2/20/40	30	No vitamin P
2/27/40	0	No vitamin P
3/ 5/40	10	No vitamin P
3/19/40	10	No vitamin P
4/ 2/40	0	No vitamin P
4/ 9/40	0	No vitamin P
5/ 4/40	6	No vitamin P
5/14/40	0	No vitamin P
5/21/40	0	No vitamin P
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6/18/40	0	No vitamin P
7/ 9/40	0	No vitamin P
7/16/40	0	No vitamin P

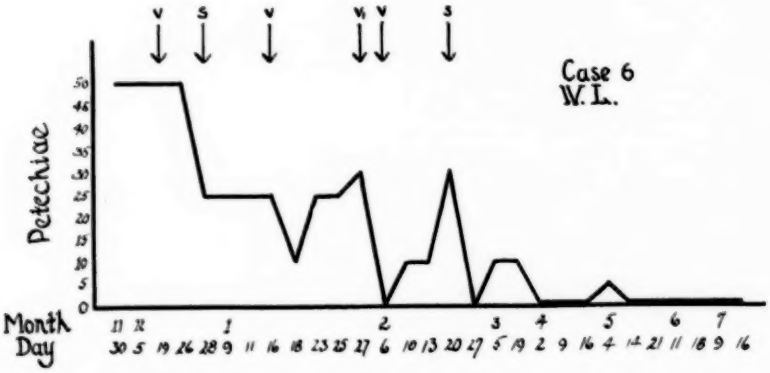

Fig. 6.—*V*, Vitamin P, 100 mg. daily; *V½*, vitamin P, 150 mg. daily; *S*, stop vitamin P.

A brief summary of data obtained on several of the twelve children studied is given in the accompanying tables and illustrations.

DISCUSSION

It is of interest to note that Cases 3 and 6 failed to respond to 100 mg. of vitamin P daily, necessitating an increase to 150 mg. daily orally. However, the vast majority of the children tested showed normal levels

following treatment with but 100 mg. of vitamin P daily. The high percentage (49) of abnormal capillary fragility found in this group of 100 allergic children is but corroborative of Manwaring's[13] belief that "increased specific capillary permeability will be shown to be the dominant fundamental physiologic change in protein sensitization to which all other anaphylactic reactions are secondary." In a previous study of a group of "normal" children, only twenty-six of 110 children, or 23.6 per cent, were found to show excessive capillary fragility as induced by a positive pressure test.

CONCLUSIONS

Capillary fragility in a group of 100 allergic children was studied by means of a positive pressure test. Forty-nine per cent had abnormal capillary fragility. In a subsequent, more detailed study, twelve children with repeated abnormal capillary fragility tests were given vitamin P and followed periodically for at least six months. In all of the twelve children, the capillary fragility tests became normal following vitamin P administration.

Vitamin P apparently plays an important role in the mechanism of permeability of the capillary wall, probably acting as an essential constituent for normal capillary permeability.

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7 West 96th Street

CAPILLARY RESISTANCE IN RHEUMATIC CHILDREN

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THIS study concerns capillary resistance as determined in 150 ambulant rheumatic children over a two-year period at the New York Post-Graduate Hospital. A total of 1,140 determinations were made between Sept. 7, 1938, and June 29, 1940, no readings being taken during July and August.

Capillary resistance is the minimal amount of suction which produces one petechia or more when applied for one minute to the skin of the forearm just below the antecubital fossa. Intervals of 5 cm. of mercury suction were used. The instrument was a suction cup apparatus, a modified Dalldorf resistometer. A description of the technique employed may be found elsewhere.[1]

GENERAL FACTORS AFFECTING CAPILLARY RESISTANCE

Various factors are considered here with relation to capillary resistance: viz., age, sex, normal differences existing in both arms, seasonal (monthly) variations, relation to weather and to the antistreptolysin titers of the patients' blood, analysis of capillary resistance in patients who showed reactions to injections of hemolytic streptococcus filtrate used in therapy, and finally, differences in capillary resistance in the treated and untreated groups.

Age.—Normally capillary resistance varies primarily with age[1-3] and season.[4] It diminishes with age from 50+ cm. in the newborn infant[2] to 15 to 20 cm. in adults. Values of 5 and 10 cm. are abnormal at any age. Elliott[5] considers even 15 cm. abnormal. The value 15 cm., abnormal during the first five years of life, becomes a borderline or questionable one in children between 6 and 15 years of age.

However, this value is so commonly encountered in older children during the winter and spring as to arouse speculation on its significance during these months. In late summer it is unusual to find capillary resistances of 15 cm. in healthy children between the ages of 6 and 15; it may be that such a value should be considered abnormal at this season.

Season.—Seasonal variations in capillary resistance are marked. Roberts and co-workers[4] have shown that capillary resistance averaged 16.5 cm. in April and 23 cm. in August in eighty-five institution children in Chicago. We have reported[1] averages of 13.2 cm. in February and 24 cm. in September in 100 rheumatic children.

This work has been carried out at the Pediatric Cardiac Research Clinic at the New York Post-Graduate Hospital of Columbia University and financed by the John and Mary R. Markle Foundation.

Differences in Arms.—Normal differences in capillary resistance exist in the two arms. Roberts and co-workers[4] have found average resistances slightly lower in the right arm. This finding has been confirmed in our study.

Hour.—Roberts has noted, furthermore, that resistances were lower as the day advanced. To control this factor, all readings in our study were made between 10 A.M. and 12 noon. The figures given by Roberts and her co-workers for twenty-three subjects tested before arising, in midmorning, and late in the afternoon were, respectively, right arm, 23.2, 21.3, and 19.3 cm.; and left arm, 25.4, 20.4 and 20.8 cm.

Vitamin C.—The relationship of ingested vitamin C to capillary resistance has been discussed frequently. Earlier papers[6-11] had claimed a direct relationship between low capillary resistance and subnormal intake or absorption of vitamin C. More recent controlled experimental evidence has shown little or no relationship in any large group between either ingested vitamin C or blood ascorbic acid values and capillary resistance.[2, 12-23]

Vitamin D.—Vitamin D has been claimed by Weld[12] as a factor in raising capillary resistance. It would be desirable to have this work confirmed.

Diseases.—Certain diseases have been shown to be associated with low capillary resistance; viz., scarlet fever,[1, 24] measles,[25] thrombocytopenic purpura hemorrhagica,[26, 27] allergic purpura,[28] ulcer and colitis,[29] and scurvy.[6-9]

There is also evidence to indicate that streptococcus toxin is an important factor in lowering capillary resistance in scarlet fever, the most toxic patients having the lowest capillary resistance.[1] The question has been raised also whether streptococcus toxin may not account for the general sudden drop in capillary resistance in the late fall noted by Roberts and associates.

PROCEDURE

Capillary resistances were determined on from four to twenty-five rheumatic children each Saturday morning for two years, except during July and August. Only left-arm computations were used for the purposes of this study. In 233 additional right-arm readings made on the same children, the average capillary resistance was found to be 1.3 cm. lower.

The average age of the 150 rheumatic children tested was 10.5 years. They ranged from 2 to 17 years, the great majority (137) being from 8 to 15 years inclusive.

The sex of these rheumatic children was: females, 77; males, 73. By sex, the average age was: females, 10.4 years; males, 10.6 years.

Analysis of Findings.—For the ten months of testing, the average capillary resistance in these 150 rheumatic children was 17.4 cm.

TABLE I

CAPILLARY RESISTANCE BY MONTHS

DATE	NO. OF PATIENTS	NO. OF READINGS	AVERAGE CAPILLARY RESISTANCE (CM.)	DATE	NO. OF PATIENTS	NO. OF READINGS	AVERAGE CAPILLARY RESISTANCE (CM.)	TWO-YEAR AVERAGE			
								MONTH	NO. OF PATIENTS	TOTAL READINGS	CAPILLARY RESISTANCE (CM.)
Sept., 1938	23	40	24.7	Sept., 1939	17	17	21.5	Sept.	40	57	23.3
Oct., 1938	32	107	25.0	Oct., 1939	28	52	18.2	Oct.	60	159	21.9
Nov., 1938	37	91	21.3	Nov., 1939	33	59	17.2	Nov.	70	150	19.4
Dec., 1938	22	46	19.2	Dec., 1939	30	51	15.1	Dec.	52	97	16.9
Jan., 1939	30	35	16.4	Jan., 1940	36	43	15.9	Jan.	66	78	16.1
Feb., 1939	34	38	13.7	Feb., 1940	33	42	14.7	Feb.	67	80	14.2
Mar., 1939	43	45	15.0	Mar., 1940	37	47	13.3	Mar.	80	92	14.2
Apr., 1939	39	44	15.8	Apr., 1940	29	31	14.1	Apr.	68	75	15.2
May, 1939	39	40	15.9	May, 1940	24	25	14.0	May	63	65	15.3
June, 1939	11	11	18.2	June, 1940	37	43	17.1	June	48	54	17.4

(Table I). At the average of the group (10.5 years) the resistance was considerably below that for nonrheumatic children, as determined by the combined cases of Abt and associates[2] and Brown[1] (see Fig. 1). These two latter groups were general pediatric clinic cases and children seen in general office practice. At the age of 10.5 years their average capillary resistance was approximately 24 cm., a figure arrived at by striking an average between the capillary resistance of the 8- to 10-year (21.8 cm.) and the 11- to 15-year groups (27 cm.). The resistances of our rheumatic children were about 6.6 cm. lower.

TABLE II

CAPILLARY RESISTANCE AT VARIOUS AGES AND AGE GROUPS IN RHEUMATIC CHILDREN

AGE (YR.)	NO. OF PATIENTS	NO. OF MONTHLY READINGS	CAPILLARY RESISTANCE (CM.)	AGE GROUP (YR.)	NO. OF PATIENTS	NO. OF READINGS	AVERAGE CAPILLARY RESISTANCE (CM.)
2	1	1	45	2-7	26	76	19.9
3	1	1	15				
4	1	7	17				
5	3	4	20				
6	5	14	22				
7	15	49	18				
8	15	53	21	8-10	39	168	19.0
9	8	62	14				
10	16	53	19.5				
11	25	84	19.7	11-15	83	400	19.1
12	13	64	17.3				
13	26	136	18.6				
14	9	55	20.4				
15	10	61	20.2				
16	1	1	15				
17	1	1	10				

Because seasonal variations are considerable, one should always give the season or month of the determination in stating capillary resistance. Roberts and co-workers have found the highest resistances for institution children in Chicago in July and August. Analysis of resistance in private patients in New York, including rheumatic children, has confirmed this finding. However, even if due allowance is made for higher resistances in the two summer months omitted in this study, bringing the twelve-month average to an estimated 18+ cm., the average capillary resistance in these 150 rheumatic children is still well below that of the general nonrheumatic group. There was little difference noted in capillary resistance due to sex: males, 19 cm.;* females, 19.3 cm.*

It is rather remarkable that the three age groups among these rheumatic children—2 to 7 years, 8 to 10 years, and 11 to 15 years—show practically the same capillary resistances (Table II). This is in contrast to the varying figures found in general practice (Fig. 1). If future investigation should bear out this uniformity of capillary re-

*The reason for the higher figures, 19 and 19.3 cm., over the average of all cases, 17.4 cm., is the greater number of single readings taken during the months of comparatively high capillary resistance (September and October).

sistance in the various age groups of rheumatic children, it would point to the conclusion that rheumatic disease in children causes a fairly low and uniform capillary strength.

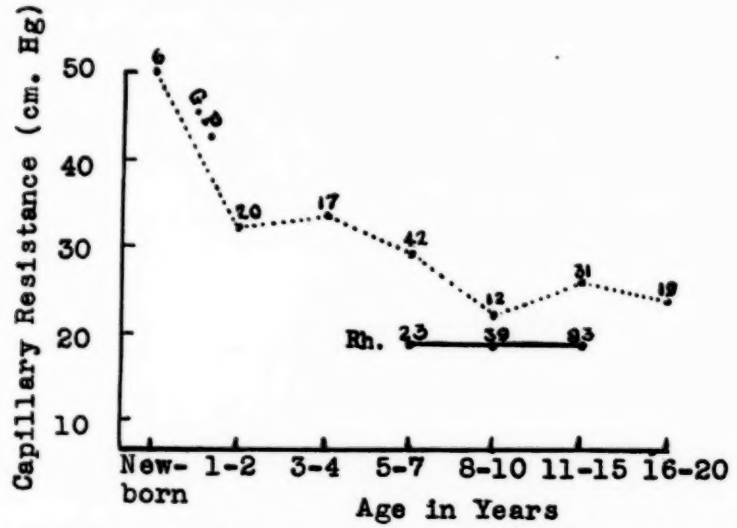

Fig. 1.—Capillary resistance by age groups. *G.P.*, Patients from general practice; combined cases of Abt and associates and Brown. *Rh*, Rheumatic children in this study. The numbers within the graph represent the number of cases.

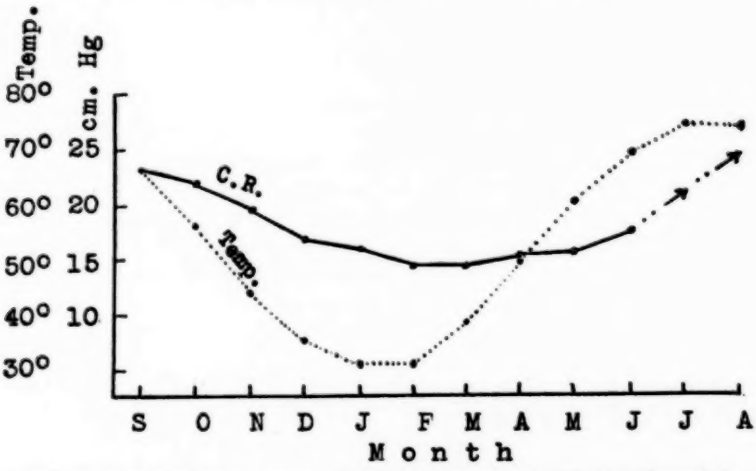

Fig. 2.—Mean temperature versus capillary resistance in rheumatic children in New York City. The arrows indicate the direction of the capillary resistance during July and August, as determined for institution children by Roberts and co-workers.

Weather.—When the average weekly capillary resistances were compared, it was observed that sudden marked changes occasionally took place. Many factors were considered to account for this; among them

were obvious infections, increased or decreased vitamin intake, group constipation, and group fatigue. However, none of these factors was common to the entire group.

The only common factor was weather. Studying its possible influence, we observed a highly consistent parallel between the average monthly capillary resistance and the average monthly temperatures in New York City (Fig. 2).

The curve of capillary resistance by months showed a drop in October, coincident with the drop in temperature at that time. This drop in resistance continued to February; the level remained unchanged in March, although temperatures were then rising. As the temperature rose to a peak in July, the capillary resistance followed in the same direction. When the temperature had already reached its peak in July and August, the capillary resistance continued to rise slightly and did not tumble until after the chilling weather of September and October. It will be observed that at the high and low temperature points, there was a slight lag between changes of temperature and changes in capillary resistance. Perhaps this can be explained by the increased production of streptococcus toxin in the fall following chilling of the body, the drop in capillary resistance lagging behind the chilling temperatures. The low resistance continues beyond the rising temperatures of February and March, chilling temperatures and rheumatism apparently not subsiding until the distinctly warmer weather of May and June. The heat of July and August, corresponding considerably to temperatures in Porto Rico where rheumatism is almost unknown, may limit and almost inhibit the growth of the streptococcus, and capillary resistance continues to rise along with peak health until the chilling weather in the fall.

When followed at weekly intervals, the relation of capillary resistance to temperature was not so constant. On thirteen occasions when there was a general marked drop in capillary resistance, this was checked against temperature. Eleven times the temperature had fallen; twice it was higher. On thirteen other occasions when the capillary resistance was generally higher, there were eleven rises in temperature and two drops. For control purposes the temperature was also checked when no marked fluctuation in capillary resistance took place; it showed no drop on any of these occasions, but rose eight times. Marked barometric fluctuations (storms) were also associated with lower capillary resistance. A sudden drop in barometric pressure would offset the favorable effects of a rise in temperature. Those weather factors which favored increased capillary resistance were rise in temperature, equability of temperature and barometric pressure, and steady high barometric pressure. Petersen[30] has done voluminous research on the relation of weather to capillary change. He has called attention to capillary dilatation during a drop and capillary spasm during a rise in barometric pressure.

Fig. 3 shows the percentage of abnormal capillary resistance readings obtained during the various months. Only distinctly abnormal values, 5 cm. and 10 cm., were considered. The ratio of these readings to the total readings taken is shown.

A sharp peak of definitely abnormal readings was reached in February (40 per cent), after a steady rise from a low of 5 per cent in September. From February, a decline in abnormal readings was noted until June (21 per cent). Analysis of the incidence of abnormal capillary resistance by months recalls the somewhat similar incidence noted for attacks of rheumatic fever.[31, 32]

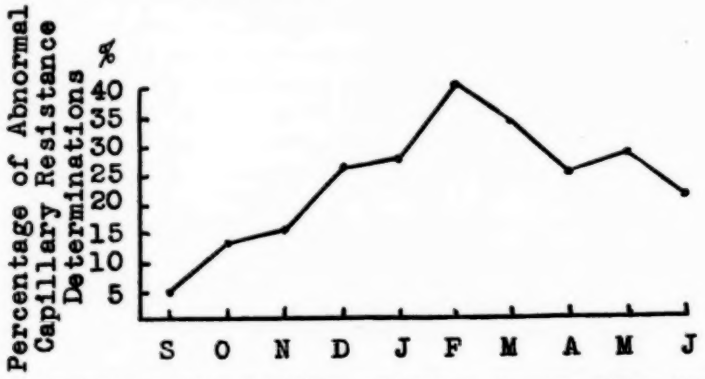

Fig. 3.—Incidence of abnormal capillary resistances in rheumatic children during various months.

In fact, temperature seems directly related to the incidence of many streptococcal diseases (scarlet fever,[33] rheumatic fever, erysipelas[34]). Thus, there are fewer cases in the warm months, July and August, and there are proportionately fewer cases as one approaches the tropics.[31, 32] Apparently the activity of streptococci diminishes as one approaches the tropics; this is proved by the fact that the antistreptolysin titer diminishes.[35]

In rheumatic fever Coburn[31] has found the highest peak of cases for New York in the early spring. Mills[32] has made a graph for Cincinnati showing a peak incidence of new cases in March and a minimum in August and September. This corresponds considerably to our graph (Fig. 3). Mills related the sharp changes in incidence to weather factors; his graph shows the same lag between change of temperature and incidence of rheumatic fever (Fig. 2) that we have observed between change of temperature and change in capillary resistance.

It was interesting to observe that on one day when there was a generally low capillary resistance followed by a marked drop in barometric pressure, seven out of twelve children treated[36] showed severe reactions to injections of streptococcus filtrate. In one patient an attack of rheumatic fever followed. These reactions are noteworthy in view of

the fact that only twelve severe reactions were recorded in the entire two years of treatment (405 injections). The question of contamination was considered, but injections of the same material the following week brought no further reaction. In view of Petersen's finding of capillary dilatation with a barometric drop, and with resistances for the group being already low (13 cm.), is it not likely that the filtrate, a streptococcus toxin, rapidly penetrated through all vessels of the body, causing the reactions noted?

To determine whether treatment of the rheumatic children affects their capillary resistance, comparisons were made between treated and untreated cases. The average resistance of forty-one patients treated for at least one year was 17.9 cm. at an average age of 11.7 years, as compared with an average of 17.4 cm. for all patients, with an average age of 10.5 years. This slight increase in capillary resistance seemed insufficient to have significance. However, the resistance of twenty-seven patients (average age, 12.6 years) treated for two years was 19.4, a possibly significant increase of 2 cm. over the average of the entire group of 150 rheumatic children.

A possible relationship was sought between capillary resistance and such blood findings as the sedimentation rate, bleeding time, coagulation time, and hemoglobin. Graphs representing monthly averages were prepared. Considerable correlation could be found, especially in relation to the sedimentation rate and bleeding time, and this will be reported soon.

Capillary resistance was also studied with relation to forty-two antistreptolysin titers made during the same months. Since the higher antistreptolysin titers are found in more active rheumatic disease, low capillary resistance was expected to accompany abnormal titers. Among twenty-two distinctly abnormal titers (more than 100 units), the average capillary resistance was 14.2 cm., in contrast to 15.6 cm. among twenty titers of 100 units or less. This suggests the possibility that the greater amount of streptococcus toxin producing the higher titers also damages the capillaries and lowers their resistance. The small number of cases and the slight difference, however, do not allow definite conclusions on this subject at present.

CONCLUSIONS

The average capillary resistance of 150 rheumatic children was low.

Seasonal variations were definite in direction and were marked.

The considerable decrease in capillary resistance which normally occurs with increasing age does not exist in rheumatic children.

Capillary resistance may be related to weather factors.

Severe reactions to injections of streptococcus filtrate may be related to low capillary resistance and weather.

A slight increase in capillary resistance was noted in the treated over the untreated rheumatic children.

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THE FORMOL-GEL TEST DURING RHEUMATIC FEVER OF CHILDHOOD

Comparison With the Sedimentation Rate and the Weltmann Reaction

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SINCE Gaté and Papacostas, in 1920,[1] found that the addition of formaldehyde to some pathologic sera produced gelation, the formol-gel test has been studied in various diseases. Recent investigations by Wise and Gutman[2] and Bing[3] have established the fact that the gelation is the result of a hyperglobulinemia, and deVries[4] stated that a positive formol-gel reaction points to a globulin value of 3.7 per cent or more. Thus the test has been advocated as a simple method of detecting hyperglobulinemia, so that both empirically and on a scientific basis, it is of diagnostic importance in multiple myeloma,[5-7] leishmaniasis,[8-10] and lymphogranuloma inguinale.[11, 12]

A number of investigators have reported on the formol-gel reaction in subacute bacterial endocarditis and rheumatic fever. Kürten,[13] in 1,100 examinations, found a positive reaction in thirty-three of thirty-five cases of endocarditis lenta and concluded that the test was of diagnostic significance. His observations were confirmed by May,[14] who obtained positive formol-gel tests in seven of eight cases of endocarditis lenta and negative reactions in thirty-four cases of fresh or recurrent rheumatic endocarditis among 210 sera examined. The latter suggested that the formol-gel test was of value in differentiating between endocarditis lenta and rheumatic endocarditis. Giraud and his co-workers,[15] and Troisier and Bariéty,[16] among others, also found the formol-gel test to be positive in endocarditis lenta. Pfeffer,[17] however, could obtain a positive reaction in only two of eight cases, and Reichel, Bettelheim, and Brandt[18] found positive formol-gel tests in only five of twenty-seven cases of endocarditis lenta, in all of which blood cultures positive for nonhemolytic streptococci were obtained. These authors questioned the diagnostic criteria used by Kürten. Vivoli,[19] on the other hand, stated the test to be frequently positive in recurrent endocarditis.

There have been several recent reports dealing with the formol-gel test in rheumatic fever. Green, Thomson, and Glazebrook[20] concluded that the formol-gel test is of value in supplementing the erythrocyte sedimentation rate in acute rheumatism. They found a high percentage of positive formol-gel tests in patients with rapid sedimentation rates.

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Schultz and Rose[21] suggested that the formol-gel test may be a valuable aid in determining the presence of active carditis in patients known to be suffering from rheumatic fever. Among their conclusions, these authors stated, "In rheumatic children, regardless of the presence of arthritis, strongly positive gel reactions are observed only when severe, active carditis is present. . . . Negative results, on the other hand, indicate the absence of severe carditis and are of favorable diagnostic import."

During the course of studies on the Weltmann reaction and sedimentation rate in rheumatic fever of childhood,[22] we had performed the formol-gel test on a number of children but had discarded the procedure because we had concluded that it was of little diagnostic or prognostic value. Children with severe rheumatic carditis frequently had negative formol-gel reactions, and some with rheumatic arthritis without evidence of carditis had positive tests. In view of the significant report of Schultz and Rose, we reinvestigated the formol-gel test in a new series of children with rheumatic fever and compared it with the sedimentation rate and Weltmann reaction.

MATERIAL AND METHODS

The children in this study were observed at the Cook County Children's Hospital and the outpatient department of the Cook County Hospital. The sedimentation rate was determined by the method of Wintrobe and Landsberg[23] and corrected according to the red cell volume by the use of their chart. The values taken for the normal red cell volumes were those reported by Mugrage and Andresen.[24] Blood for the Weltmann reaction and formol-gel test was allowed to clot in paraffin-lined tubes to minimize hemolysis. The Weltmann reaction (coagulation band of the serum) was determined by Weltmann's original technique.[25, 26] The formol-gel test was performed by adding 2 drops of Merck's formaldehyde (37 per cent) (made neutral to phenolphthalein with a 20 per cent solution of sodium carbonate), to 1 c.c. of serum in a small test tube. The contents of the tube were shaken, and the tube was allowed to remain in an inclined position[27] for twenty-four hours at room temperature. Although both gelation and opacity were observed, only the latter will be discussed.

In determining the degree of gelation, we followed the suggestions of Gutman and Wise,[28] but we did not adhere to the interpretation of Schultz and Rose.[21] The latter authors designated a ++, +++, or ++++ result as a strongly positive reaction. In discussing our results, we refer to a ++ test as weakly positive, and a +++ or ++++ result as a strongly positive reaction.*

*The formol-gel test was interpreted as follows: No increase in viscosity, – negative; questionable increase in viscosity, ± negative; increased viscosity, + doubtful; very viscous flow, ++ weakly positive; semisolid, +++ strongly positive; solid, ++++ strongly positive.

The patients were divided into two groups. One group consisted of children who were attending the cardiac clinic and served as the control series. These children had definite cardiac lesions of known rheumatic origin (they previously had been in the Cook County Children's Hospital ill with rheumatic fever), but they showed no clinical manifestations of persisting rheumatic infection. They were daily attending the regular schools or special institutions in Chicago. The second group was made up of children ill with rheumatic fever in the Cook County Children's Hospital. In this group, tests were made as soon as possible after admission to the hospital, and in a certain number of these children repeated tests, usually once or twice weekly, were made during their hospital stay.

RESULTS

Eleven children with rheumatic heart disease, but without evidence of infection at the time, made up the control group. The results are shown in Table I. In eight of these children the corrected sedimentation rate was normal, and in three it was slightly elevated. The Weltmann reaction was normal in eight and very slightly increased in two, while the formol-gel test was negative in all eleven.

TABLE I

CONTROL GROUP OF ELEVEN CHILDREN WITH RHEUMATIC HEART DISEASE, BUT WITHOUT EVIDENCE OF INFECTION

AGE	RACE	SEX	CLINICAL DIAGNOSIS	SEDIMENTATION RATE (MM.)	RED CELL VOLUME	CORRECTED SEDIMENTATION RATE (MM.)	WELTMANN REACTION	FORMOL-GEL
8	N	F	Mitral insufficiency	9	42	10	6	-
11	W	M	Mitral insufficiency	2	46	6	6	-
9	W	F	Mitral insufficiency	5	38	2	6½	-
12	W	M	Mitral insufficiency	20	42	20	6	-
10	W	F	Mitral insufficiency	20	41	19	6	±
13	W	M	Mitral insufficiency	5	44	6	6	-
11	N	F	Mitral insufficiency	11	42	11	6½	-
12	W	F	Mitral insufficiency and stenosis	12	42	12	7	-
5	N	M	Mitral insufficiency and stenosis	19	41	20	6½	-
18	W	M	Mitral stenosis; auricular fibrillation	8	47	8	5½	-
13	W	M	Aortic insufficiency and stenosis	6	46	8	7	-

Sixty-four children ill with rheumatic fever were also observed. In this group a total of 329 determinations were made. Table II indicates the results obtained at the initial observation made on each case, as soon as possible after admission. The axillary temperature and pulse rate indicated are the highest noted during the twenty-four-hour period in which the sedimentation rate, Weltmann reaction, and formol-gel test

TABLE II

INITIAL VALUES OF SEDIMENTATION, WELTMANN, AND FORMOL-GEL TESTS IN CHILDREN ILL WITH RHEUMATIC FEVER

CASE NO.	AGE	SEX	RACE	CLINICAL DIAGNOSIS	AXILLARY TEMPERATURE	PULSE RATE	SEDIMENTATION RATE (MM.)	RED CELL VOLUME	CORRECTED SEDIMENTATION RATE (MM.)	WELTMANN REACTION	FORMOL-GEL
1	12	F	W	Chorea; heart normal	98.6	84	7	42	7	6	-
2	11	F	W	Chorea; heart normal	98	82	14	45	17	9	-
3	11	M	W	Chorea; heart normal	98.6	80	10	42	10	8	-
4	10	F	W	Chorea; heart normal	98.8	88	8	48	15	6	±
5	8	M	W	Chorea; heart normal	98.2	90	33	40	32	7½	-
6	9	F	N	Chorea; heart normal	99	94	38	41	38	5	-
7	10	F	W	Chorea; heart normal	98.6	100	25	40	24	6	-
8	9	F	W	Chorea; heart normal	98.8	82	4	47	10	9	-
9	11	F	W	Chorea; heart normal	98.4	96	23	42	23	8	-
10	9	F	W	Arthritis; chorea; heart normal	100.6	120	54	35	42	3	+
11	8	M	W	Arthritis; chorea; heart normal	99.6	108	55	36	43	2	+
12	4	F	N	Arthritis; heart normal	101.4	130	14	26	25	½	+ + + +
13	13	M	W	Arthritis; heart normal	101	104	47	45	50	4	+ + + +
14	8	M	W	Arthritis; heart normal	99.2	92	62	33	43	½	+ + + +
15	9	F	W	Arthritis; heart normal	101	100	56	38	50	0	-
16	8	F	W	Arthritis; heart normal	99	100	58	35	45	1	-
17	9	M	W	Arthritis; heart normal	99	110	54	39	50	0.	-
18	12	M	W	Arthritis; heart normal	101.2	118	56	38	48	2½	+
19	10	M	W	Arthritis; heart normal	101	136	63	30	36	4	+
20	8	M	W	Arthritis; heart normal	98	110	50	41	50	3	+ + + +
21	13	M	W	Arthritis; heart normal	99.2	114	52	35	36	5	+ +
22	13	M	W	Arthritis; heart normal	99	96	47	43	47	9	±
23	11	M	W	Arthritis; heart normal	101	138	35	43	36	3	±
24	4	M	W	Arthritis; heart normal	100.6	102	53	40	51	½	-
25	13	F	W	Arthritis; heart normal	98	70	49	41	46	4½	+ + + +

26	9	F	W	Arthritis; chorea; mitral insufficiency	98	84	54	37	45	6	+++
27	9	M	N	Arthritis; chorea; mitral insufficiency	99	86	50	39	45	5	+
28	12	M	W	Arthritis; aortic insufficiency	101.6	130	60	31	38	0	-
29	10	M	N	Arthritis; mitral insufficiency	98.8	110	46	42	46	6	+++
30	11	M	W	Arthritis; mitral insufficiency	101.4	110	56	36	43	4½	-
31	13	M	W	Arthritis; mitral insufficiency	101.4	120	51	41	47	2	-
32	14	M	W	Arthritis; mitral insufficiency	100	110	63	30	34	4	++++
33	6	M	W	Arthritis; mitral insufficiency	100.2	110	62	32	43	1½	++++
34	8	M	W	Arthritis; mitral insufficiency	99	100	61	32	40	2	-
35	7	F	W	Arthritis; mitral insufficiency	99.6	92	58	38	54	3	-
36	11	M	W	Arthritis; mitral insufficiency	99	120	46	42	46	4	+
37	13	M	W	Arthritis; mitral insufficiency	99	90	57	37	45	5½	++++
38	12	M	W	Mitral insufficiency; epistasis	99.4	124	35	35	22	4	±
39	7	F	W	Mitral insufficiency; erythema annulare	98.8	100	42	40	42	4½	++
40	12	F	W	Mitral insufficiency	98	90	40	41	38	5	-
41	8	M	W	Mitral insufficiency	100.4	108	52	36	42	3	-
42	7	M	W	Mitral insufficiency	99	110	53	38	48	5	-
43	13	F	N	Mitral insufficiency	99.2	100	50	28	22	5	+
44	9	M	W	Mitral insufficiency and stenosis	99	112	56	26	25	6	-
45	12	M	W	Mitral insufficiency and stenosis	100	118	59	37	50	4	+
46	11	M	W	Mitral insufficiency and stenosis	98	100	58	35	43	4	++
47	8	F	N	Mitral insufficiency and stenosis	101	132	53	38	49	2	++++
48	7	M	W	Pancarditis	101.6	130	56	36	45	0	+
49	9	M	W	Pancarditis	100.8	120	63	31	39	5	-
50	7	M	W	Pancarditis	101.2	140	60	32	40	0	-
51	4	F	N	Pancarditis	100	120	66	26	34	4	-
52	5	F	W	Pancarditis; pneumonitis	99.8	70	39	47	52	1½	±
53	11	F	W	Recurrent carditis; pneumonitis	100.2	120	49	41	47	4	-

TABLE II—CONT'D

CASE NO.	AGE	SEX	RACE	CLINICAL DIAGNOSIS	AXILLARY TEMPERATURE	PULSE RATE	SEDIMENTATION RATE (MM.)	RED CELL VOLUME	CORRECTED SEDIMENTATION RATE (MM.)	WELTMANN REACTION	FORMOL-GEL
54	13	M	W	Aortic and mitral insufficiency; slight decompensation	100.2	104	56	37	44	4½	-
55	10	M	W	Mitral stenosis; slight decompensation	102	130	39	39	28	0	-
56	13	M	W	Mitral stenosis; slight decompensation	99.6	120	60	29	31	1	±
57	11	M	N	Mitral stenosis; slight decompensation	100.4	104	63	30	35	4	+ + +
58	12	F	W	Mitral stenosis; moderate decompensation	98.6	112	23	43	26	7	+ + + +
59	12	M	W	Mitral stenosis; severe decompensation	103	140	53	31	32	3½	+
60	13	F	W	Mitral stenosis; severe decompensation	98	84	8	37	2	7	-
61	10	M	W	Mitral stenosis; severe decompensation	98.8	120	2	41	2	6	-
62	7	M	W	Mitral stenosis; severe decompensation	98.2	116	4	50	16	6	-
63	14	F	W	Mitral stenosis; severe decompensation and auricular fibrillation	98	82	23	48	30	4	-
64	7	F	N	Mitral stenosis; severe decompensation and auricular fibrillation	100	150	43	40	43	8	+ + + +

were determined. The clinical diagnoses stated are those which were made at the time of the observation, with the exception that several children who had rheumatic arthritis also had apical systolic blows on admission. These murmurs disappeared with the clinical subsidence of the infection, so they were not considered to be truly organic.

Chorea.—There were nine cases of from moderate to severe chorea without evidence of other rheumatic infection at the time of observation. In four children the corrected sedimentation rate was normal; in three it was slightly increased, and in two it was moderately increased. The Weltmann reaction was normal or increased in all but one case in which it was slightly to the left. The formol-gel test was negative in all nine children.

Arthritis.—The corrected sedimentation rate was increased in all of the fourteen children with arthritis and in the two with arthritis and chorea. The Weltmann reaction gave a shift to the left (shortened coagulation band) in fifteen of the sixteen children. In one child, the Weltmann reaction showed a shift to the right (increased coagulation band). The formol-gel test was negative in six cases, doubtful in four, weakly positive in one, and strongly positive in five. Thus, of the sixteen children with arthritis but without any clinical evidence of carditis at the time, or subsequently during their hospital stay, six, or 40 per cent, had strongly positive formol-gel tests.

Arthritis With Carditis.—In all of the ten children with arthritis and carditis and in the two children with arthritis, chorea, and carditis, the corrected sedimentation rate was from moderately to greatly increased. The Weltmann reaction showed a shift to the left of varying degree in ten cases, and it was normal in two. The formal-gel test was negative in five, doubtful in two, and strongly positive in five. In twelve children ill with arthritis and carditis the formol-gel test was, therefore, strongly positive in only five, or 42 per cent.

Carditis.—We observed sixteen children ill with carditis, but without decompensation, and all had increased corrected sedimentation rates. The Weltmann reaction gave a shift to the left in fifteen cases and was normal in one. The formol-gel test was negative in ten, doubtful in three, weakly positive in two, and strongly positive in only one child. Thus, only one, or 6.3 per cent, of sixteen children ill with rheumatic carditis without arthritis gave a strongly positive formol-gel test.

Cardiac Decompensation.—There were eleven children in this group who had varying degrees of decompensation. Some of them, as indicated, were febrile. Two had normal corrected sedimentation rates, but in the other nine the corrected sedimentation rates were increased to varying degrees. It will be noted that the observed sedimentation rate was in some cases normal, but that when the rate was corrected, it became increased because of the high red cell volume. The Weltmann reaction gave a shift to the left in six, a shift to the right in three, and a normal value in two cases. The formol-gel test was strongly positive in only three, or 27 per cent, of the eleven children.

CONCLUSIONS BASED ON SINGLE OBSERVATIONS

Of thirty-nine children ill with carditis, the formol-gel test was strongly positive in only nine, or 23.1 per cent. The corrected sedimentation rate, on the other hand, was increased in thirty-seven of the thirty-nine children, or in 95 per cent. The Weltmann reaction gave a shift to the left in thirty-one, or 79.5 per cent, of the thirty-seven cases. If the children who were decompensated are not included, we find that the corrected sedimentation rate was increased in 100 per cent of the cases; the Weltmann reaction gave a shortened coagulation band (shift to the left) in 89.3 per cent, and the formol-gel test was strongly positive in only 33 per cent. On the basis of single determinations, it appears, therefore, that the formol-gel test is of little value in corroborating the presence of carditis when it is clinically evident.

On the other hand, in fourteen children ill with arthritis, but without clinical evidence of carditis at the time of observation or subsequently during their hospital stay, the formol-gel test was strongly positive in six, or 40 per cent. Our results, therefore, indicate that, on the basis of single determinations, in a child ill with rheumatic fever a strongly positive formol-gel test does not always mean the presence of carditis, nor does a negative formol-gel test indicate the absence of carditis.

DAILY OBSERVATIONS ON REPRESENTATIVE CASES

We made frequent determinations of the Weltmann reaction, sedimentation rate, and formol-gel test, on the average of twice a week, on some of the children ill with rheumatic fever. The results were correlated with the pulse rate and axillary temperature and with the clinical sequence of events. The brief case histories are illustrated with charts.

CASE 1: *Arthritis without carditis.*—A 4-year-old colored girl was admitted to the hospital because of fever during the preceding week and pain and swelling in the right knee and ankle for two days. She gave a history of a sore throat about one week before the onset of the joint symptoms.

At the first examination the temperature was 102.6° F., and pulse rate, 120. The right knee and ankle and the left knee were tender and swollen. The heart appeared normal except for a soft systolic blow at the apex. The following day the corrected sedimentation rate was 29 mm., the Weltmann reaction ½, and the formol-gel test strongly positive.

Joint symptoms and fever rapidly disappeared under the influence of salicylates, and by the fourth hospital day the temperature was 98.6° F., and the child appeared to be comfortable and had no complaints. The formol-gel test remained strongly positive until the fifteenth hospital day and was negative thereafter. The sedimentation rate was increased and the Weltmann reaction gave a shift to the left up until the thirty-sixth day. When the child left the hospital on the fortieth day, the systolic blow had disappeared, the sedimentation rate was normal, and the Weltmann reaction was slightly to the right.

Summary: In a 4-year-old colored girl with rheumatic arthritis who was observed for forty days, the formol-gel test was strongly positive for the first fifteen days, although there was no evidence of carditis during the child's stay in the hospital.

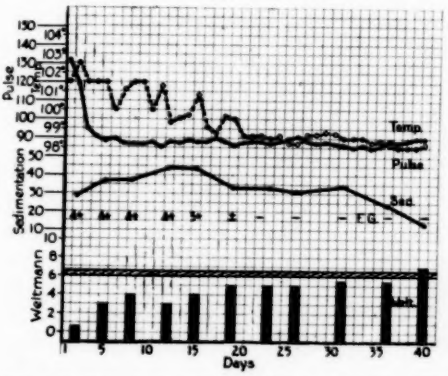

Fig. 1.—Chart of course in Case 1, 4-year-old colored girl with arthritis, but without carditis.

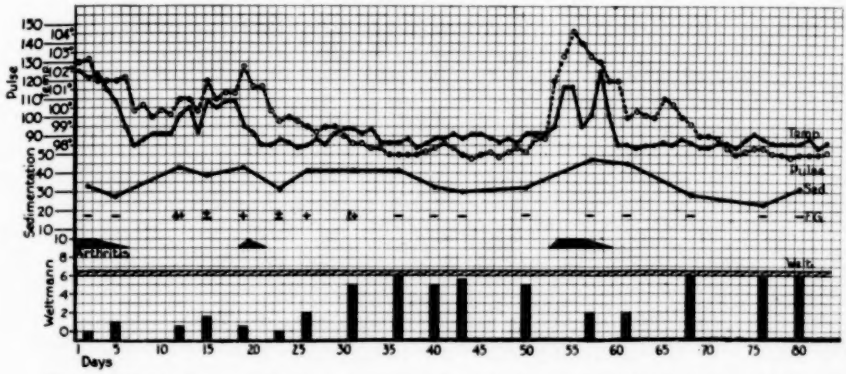

Fig. 2.—Chart of course in Case 2, 13-year-old white boy with arthritis and carditis.

CASE 2: *Arthritis with carditis.*—A 13-year-old white boy was admitted to the hospital because of pain in the right thigh and fever for two days. The past history revealed that the boy had had rheumatic fever at the age of 6 years and had remained in bed for about eight months because of "heart trouble." About three months before the present admission he had been hospitalized in another institution where he remained for two months because of joint pains; for the past month he had been in bed at home.

On admission, the temperature was 102° F., and pulse rate, 130. There was pain and swelling in both wrists and tenderness in the right knee and hip. The heart outline was boot-shaped with the left border extending out to the left anterior axillary line and the right border being 2 cm. to the right of the right parasternal line. There was a loud, blowing, diastolic murmur at the aortic area and a systolic murmur at the apex. Diagnosis was rheumatic fever with arthritis, aortic insufficiency, and possible mitral insufficiency.

The day following admission the temperature was 101.6° F.; the corrected sedimentation rate was 33 mm., the Weltman reaction zero, and the formol-gel test negative. An electrocardiogram showed left axis deviation.

During the hospital stay of eighty-three days there were two exacerbations, with joint pains and fever. The formol-gel test was negative in fifteen of the seventeen determinations made, and was strongly positive only once, on the twelfth day. The corrected sedimentation rate fluctuated but was never normal during the whole period. The Weltmann reaction was relatively normal for a short time after the first exacerbation but shifted to the left again during the second exacerbation of fever and arthritis, during which there was also a marked rise in the sedimentation rate.

When the patient went home on the eighty-third day, he had been afebrile for the previous twenty-four days. The Weltmann reaction had returned to normal, but the sedimentation rate was still increased and the formol-gel test was negative.

Summary.—A 13-year-old white boy with arthritis and carditis was observed for eighty-three days. Despite the presence of aortic insufficiency, cardiac enlargement, and two exacerbations of fever and joint symptoms, the formol-gel test was strongly positive in only one of seventeen examinations.

CASE 3: *Arthritis with carditis.*—A 13-year-old white boy was admitted to the hospital from a boys' school, with complaints of pains in various joints for four weeks, shortness of breath and pain over the heart for three weeks, and swelling of the abdomen for one week.

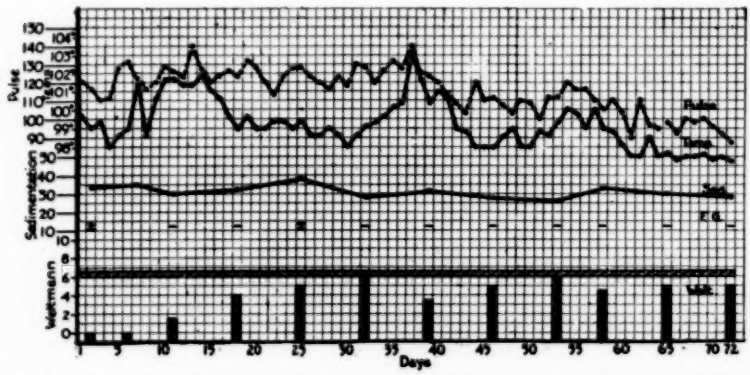

Fig. 3.—Chart of course in Case 3, 13-year-old white boy with rheumatic arthritis and marked carditis.

On admission, the temperature was 101.2° F., and pulse rate, 120. The essential physical findings were enlargement of the heart to the left anterior axillary line, apex beat in the sixth interspace, presystolic thrill and double mitral murmur, crepitant râles in both lower pulmonary lobes, palpable spleen and liver, café-au-lait color, with marked pallor and no petechiae. The red blood count was 2,870,000; hemoglobin, 7.5 Gm.; white blood count, 11,200; polymorphonuclear cells, 74 per cent. The diagnostic impression at the time was possible subacute bacterial endocarditis.

The Weltmann reaction on the day following admission gave a value of zero, the sedimentation rate was markedly increased, and the formol-gel test was negative. The marked shift to the left in the Weltmann reaction was interpreted as strong evidence against the possibility of subacute bacterial endocarditis. Four blood cultures subsequently taken at weekly intervals were negative.

The clinical course was one of carditis. The pulse was rapid most of the time and the temperature was rarely normal. At the end of seventy-two days, the boy was sent to a convalescent home, having been afebrile for nine days and being considerably improved. There were two definite exacerbations, with increased fever and precordial pain which were associated with shifts to the left in the Weltmann reaction. The sedimentation rate was moderately increased during the whole hospital stay, but the formol-gel test, performed twelve times, was never strongly positive.

Summary.—A 13-year-old white boy with rheumatic arthritis and marked carditis was observed for seventy-two days. During this time the clinical picture was one of active carditis. The Weltmann reaction showed phases of exudative activity and the sedimentation rate was always moderately increased, but the formol-gel test was at no time strongly positive.

CASE 4: *Carditis.*—A 13-year-old colored girl had had "heart trouble" for four years. There were frequent sore throats, and one day before hospitalization she developed a fever.

On admission, the temperature was 103° F., and pulse rate, 124. She was weak and emaciated. The tonsils were large and cryptic. The heart was enlarged to slightly beyond the left anterior axillary line and there were presystolic and systolic murmurs at the apex. She remained in the hospital for forty-seven days and was taken home against our advice.

During the period of observation, the clinical course was one of carditis associated with a marked anemia, moderate liver enlargement, gallop rhythm, and progressive cardiac enlargement. There were two severe bouts of epistaxis, one on the third and the other on the seventeenth hospital day. The second epistaxis was associated with a marked rise in temperature and severe precordial pain.

The corrected sedimentation rate was persistently increased at about the same high level, and the Weltmann reaction gave a shift to the left during the entire period of forty-seven days. The formol-gel test, however, was negative until the fortieth hospital day, when it became strongly positive, at a time when there was some clinical improvement.

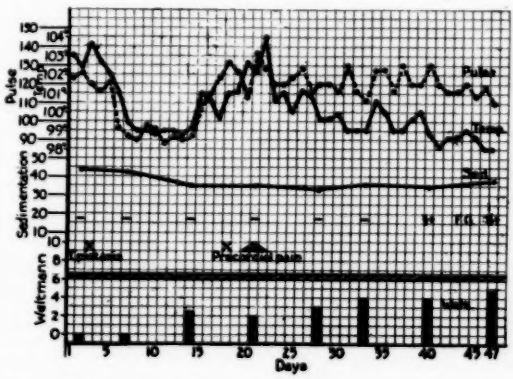

Fig. 4.—Chart of course in Case 4, 13-year-old colored girl with rheumatic carditis.

Summary.—In a 13-year-old colored girl with severe rheumatic carditis in whom the sedimentation rate was always very rapid and the Weltmann reaction was to the left, the formol-gel test became strongly positive for the first time toward the end of the period of observation when there was slight clinical improvement.

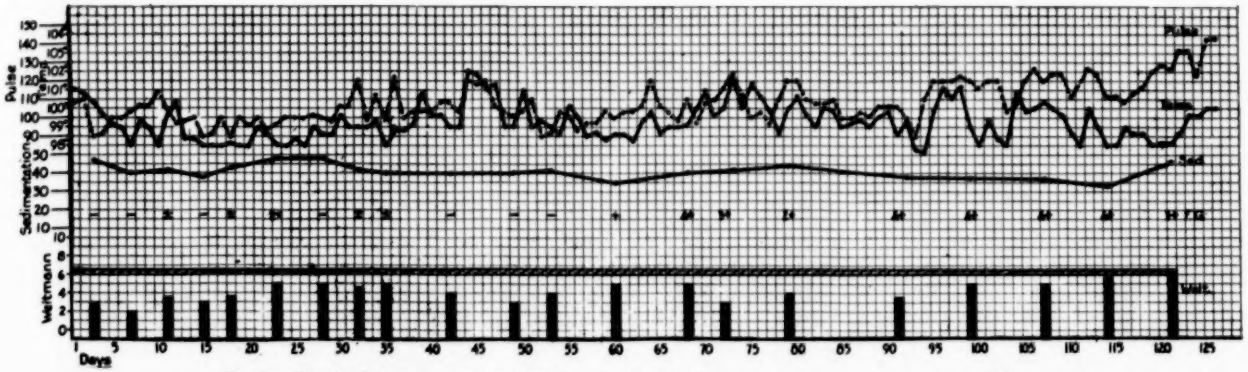

Fig. 5.—Chart of course in Case 5, 13-year-old colored boy with active rheumatic carditis.

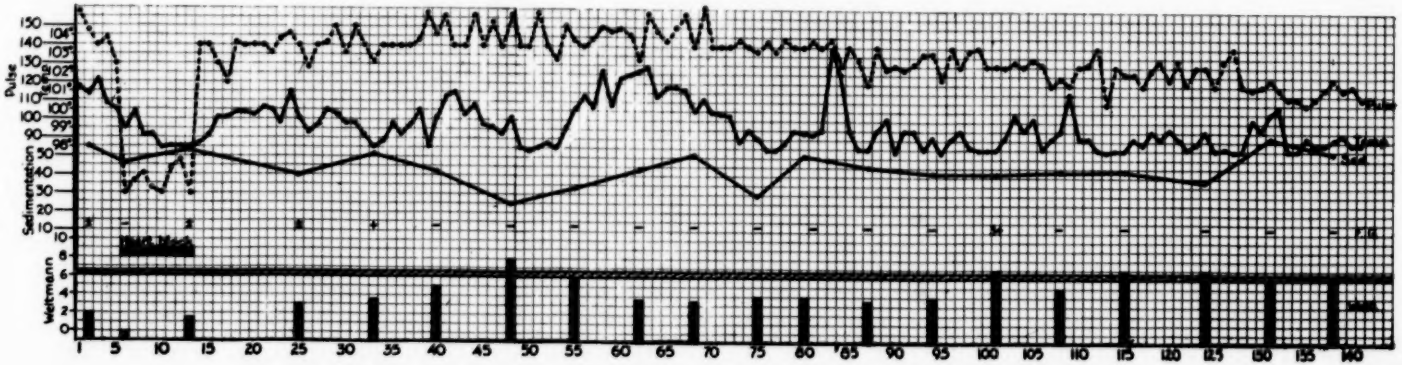

Fig. 6.—Chart of course in Case 6, 5-year-old white girl with rheumatic carditis and decompensation.

CASE 5: *Carditis.*—A 13-year-old colored boy had been complaining of headache and weakness and had seemed feverish for about five weeks before admission to the hospital.

At the first examination, the temperature was 101° F., and pulse rate, 104. The heart was slightly enlarged to the left, the apex beat was diffuse, and there was an apical systolic blow. The red blood count was 3,000,000, and the hemoglobin, 54 per cent (Sahli). On the third hospital day the corrected sedimentation rate was 47 mm., the coagulation band was 3, and the formol-gel test was negative.

The clinical course was one of progressive cardiac damage, with frequent periods of fever. Cardiac enlargement increased, and a double mitral murmur developed. The boy frequently complained of pain in the chest and was dyspneic at times. After the boy was in the hospital 127 days his parents insisted on taking him home. At the time of his discharge his temperature was 100° F., and pulse rate, 144.

The sedimentation rate was rapid throughout the period of observation. The coagulation band was to the left until eleven days before the boy went home, when it became normal despite an increasing pulse rate and a rise in temperature. The formol-gel test did not become strongly positive until the sixty-seventh hospital day, but it remained strongly positive during the rest of the period of observation.

Although the Weltmann reaction was normal when the boy went home, the sedimentation rate was rapid, and clinically he had an active carditis; we would say, therefore, that at that time he had an active rheumatic infection in which the proliferative and exudative processes were counterbalancing each other.

Summary.—A 13-year-old colored boy with active carditis was observed for 127 days. Although there was clinical evidence of carditis from the beginning of the period of observation, with a rapid sedimentation rate and the Weltmann reaction shifted to the left, the formol-gel test did not become strongly positive until the sixty-seventh hospital day. When the boy left the hospital, he still had an active carditis, but the Weltmann reaction was normal.

CASE 6: *Carditis with decompensation.*—A 5-year-old white girl had had scarlet fever followed by "heart trouble" about six months before admission to the hospital. For the previous week she had had fever, was coughing, and seemed short of breath.

When seen on admission, her temperature was 101.2° F., pulse rate 156, and blood pressure 120/88. The essential findings were slight cyanosis and marked dyspnea; enlargement of the heart to the left anterior axillary line; presystolic thrill; double mitral murmur; pericardial friction rub and moist râles in both lower pulmonary lobes. The liver was tender and enlarged to four fingerbreadths below the right costal arch, and there was slight edema of the lower extremities.

Digitalization was fairly effective at first, but on the sixth hospital day a complete heart block was noted which lasted for eight days. The child remained in the hospital for 141 days, during which time there were recurring periods of fever associated with dyspnea and increased liver enlargement; during the afebrile periods the clinical condition was improved.

The corrected sedimentation rate was always increased but tended to be at higher levels during the febrile periods and relatively lower during the afebrile periods. The Weltmann reaction gave a shift to the left on most of the examinations and correlated well with the sedimentation rate except toward the end of the hospital stay. The patient went home having a rapid sedimentation rate but normal Weltmann reaction, and was clinically greatly improved. The formol-gel test was negative in nineteen of the twenty examinations made. Only once, after the child had been in the hospital 102 days, did the formol-gel test become strongly positive.

Summary.—In a 5-year-old white girl with rheumatic carditis and periods of fever and decompensation, who was observed for 141 days, the sedimentation rate

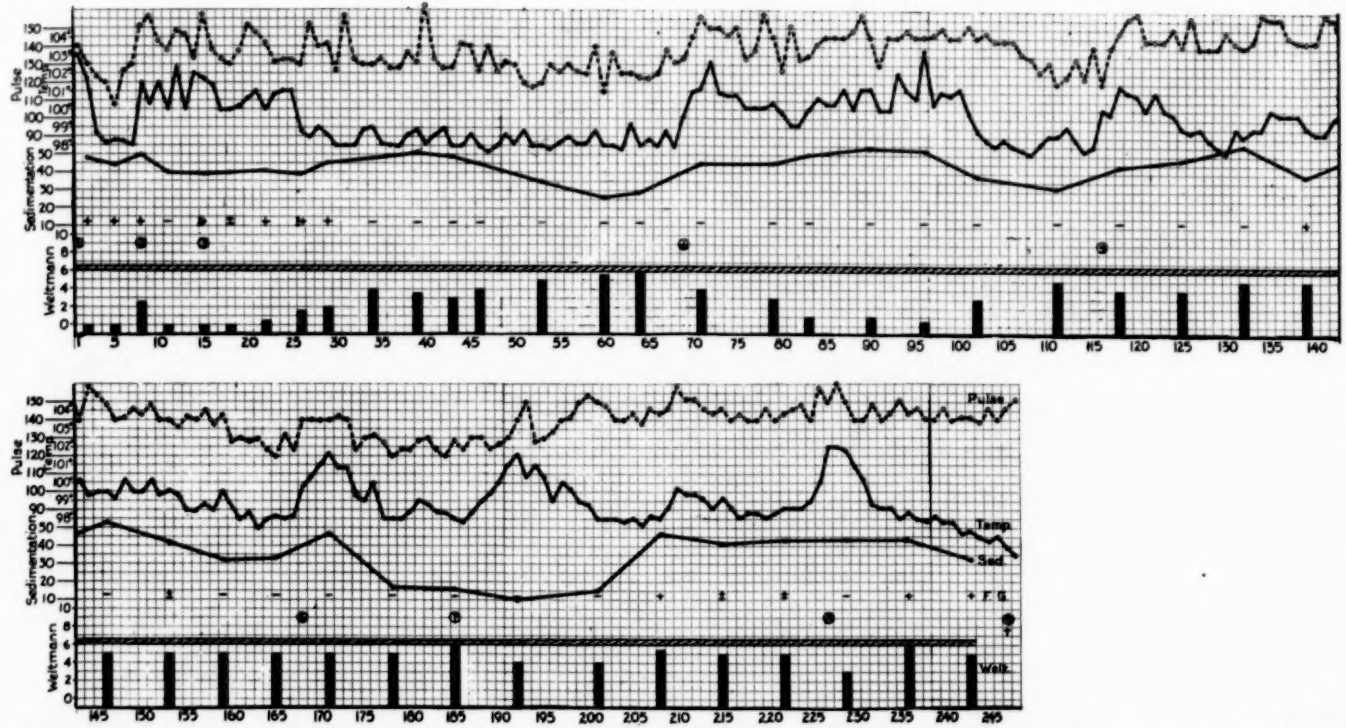

Fig. 7.—Chart of course in Case 7, 7-year-old white boy with progressive rheumatic carditis followed by death. The circled numbers refer to various episodes which are described in the text.

was always increased and the Weltmann reaction indicated prolonged periods of inflammatory activity; the formol-gel test, however, was strongly positive only once during the entire period.

CASE 7: *Carditis with death.*—A 7-year-old white boy was admitted to the hospital, with a history of having been well until two weeks previously. Since then he had begun to lose weight and to eat poorly. One week before admission he developed a fever and began to complain of abdominal pain.

The first examination (Fig. 7, *1*) showed the heart to be enlarged to slightly beyond the left anterior axillary line. There was a double apical murmur and a pericardial friction rub. The temperature was 103° F., and pulse rate, 140. On the day following admission, the Weltmann reaction was zero, the corrected sedimentation rate 48 mm., and the formol-gel test doubtful. There was some clinical improvement for several days, but a pericardial effusion developed (*2*) which was tapped on the fifteenth hospital day (*3*), and 270 c.c. of clear fluid was obtained. During this time the coagulation band remained low and the sedimentation rate rapid, while the formol-gel test became slightly positive. There then followed a period of clinical improvement toward the end of which the coagulation band became normal, the sedimentation rate relatively slow, and the formol-gel test negative. On the sixty-ninth hospital day (*4*), a febrile period began, with dyspnea and precordial and abdominal pain which lasted to the 103rd day. During this period the coagulation band became low again and the sedimentation rate more rapid, but the formol-gel test remained negative. Short phases of improvement were again followed by febrile periods (*5*, *6*), and the clinical course was progressively downhill. Decompensation ensued (*7*), and although there was an associated febrile reaction, the sedimentation rate became almost normal. During this time the formol-gel test remained negative, but the coagulation band again became lower. From the 227th to the 231st days there was a preterminal febrile episode associated with another lowering of the coagulation band; the sedimentation rate remained rapid, but the formol-gel test continued to be negative.

The boy died (*9*), after having been in the hospital 248 days. An autopsy could not be obtained.

Summary.—A 7-year-old white boy with progressive rheumatic carditis died 248 days after hospitalization. The formol-gel test in forty-two determinations was slightly positive only once and was never strongly positive. The sedimentation rate was rapid most of the time, except when decompensation was severe. The Weltmann reaction almost always gave a shift of varying degree to the left, even during some of the periods of decompensation when the sedimentation rate was relatively slow.

CASE 8a: *Pancarditis and death.*—A 5-year-old colored girl entered the hospital, with complaints of headache, weakness, abdominal pain, and vomiting for five days.

On admission, the temperature was 100° F., and pulse rate, 120. The heart was moderately enlarged to the right and left, and there were a presystolic thrill and a double mitral murmur. The corrected sedimentation rate was 40 mm., the coagulation band was 4, and the formol-gel test was negative. An electrocardiogram showed myocardial damage.

The clinical course was one of severe pancarditis. The child became increasingly dyspneic, the pulse rate mounted, and on the sixth hospital day a pericardial friction rub was heard.

On the fifth hospital day, the coagulation band and sedimentation rate were the same as on admission, and the formol-gel test became strongly positive. The child died on the tenth hospital day. Shortly before death, the coagulation band went down to 3, but the formol-gel test became only slightly positive and the sedimentation rate was relatively slower (28 mm.).

An autopsy was performed seven hours after death and the anatomic diagnosis was: (1) Acute fibrinous pericarditis; (2) recent verrucous endocarditis of the aortic valve; (3) old moderate fibroplastic deformity of the mitral valve; and (4) acute myocarditis.

Summary.—A 5-year-old colored girl died of pancarditis, after having been observed for ten days. The coagulation band gave a shift to the left during this time, and the sedimentation rate was rapid, although it became relatively slower just before death. Although the formol-gel test was strongly positive on the fifth hospital day, it was negative on admission and was only slightly positive shortly before death. (Fig. 8*A*.)

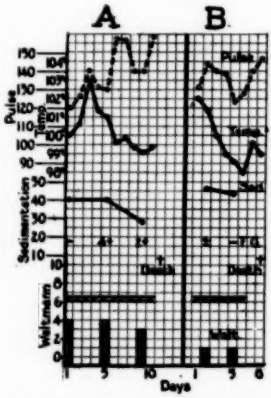

Fig. 8.—*A*, Chart of course in Case 8a, 5-year-old colored girl with pancarditis followed by death. *B*, Chart of course in Case 8b, 8-year-old white girl with pancarditis followed by death.

CASE 8b: *Pancarditis and death.*—An 8-year-old white girl entered the hospital because of pain in both feet and ankles for about three weeks, shortness of breath for two weeks, and pain in the chest for one day.

On admission to the hospital, the temperature was 102° F., and pulse rate, 120. The child was dyspneic and restless. The heart was enlarged to the left midaxillary line. The apex beat was diffuse, and there was a systolic apical murmur. The liver was palpated three fingerbreadths below the right costal margin and was moderately tender.

Although the temperature became progressively lower, the pulse rate remained rapid, and on the sixth hospital day, a pericardial friction rub was detected. The child died suddenly on the eighth hospital day. There was no autopsy.

Blood was obtained for examination on the second and fifth hospital days. On both occasions the Weltmann reaction gave a marked shift to the left and the corrected sedimentation rate was rapid, but the formol-gel test was negative.

Summary.—The formol-gel test was negative, while the sedimentation rate was rapid and the coagulation band low, in an 8-year-old girl who died of severe pancarditis, after having been in the hospital for eight days. (Fig. 8*B*.)

DISCUSSION

From our results we are unable to substantiate some of the conclusions of Schultz and Rose[21] regarding the value of the formol-gel test in rheumatic fever of childhood. These authors stated, "In rheumatic children, regardless of the presence of arthritis, strongly positive gel

reactions are observed only when severe, active carditis is present. . . . Strongly positive reactions in children or in adults without arthritis suggest the presence of carditis. Negative results, on the other hand, indicate the absence of severe carditis and are of favorable diagnostic import." In our series of sixteen children ill with arthritis in whom no clinical or electrocardiographic evidence of carditis could be obtained during their entire hospital stay, six, or 40 per cent, had strongly positive formol-gel tests at the time of the initial examinations. In several of these children, of whom the patient in Case 1 is an example, who had strongly positive formol-gel tests on admission, frequent tests were made during their hospital stay. As the arthritis subsided, the formol-gel test became negative. On the other hand, of thirty-nine children ill with carditis but without arthritis, the formol-gel test was strongly positive in only nine, or 23.1 per cent, at the initial examination. Several of the more severely ill children had repeatedly negative formol-gel tests. One boy especially, who was observed for 248 days and who died of a severe progressive carditis (Case 7), never had a strongly positive formol-gel test. Furthermore, in some cases of carditis, the formol-gel test was negative during a considerable period when carditis was obviously present and became strongly positive toward the end of the period of observation. In some children, convalescence was apparently occurring at this time.

In only one of the sixty-four cases of rheumatic fever observed did the formol-gel test appear to be of any diagnostic importance. An 11-year-old boy with recurrent rheumatic fever and aortic insufficiency had a strongly positive formol-gel test over a period of 210 days. The strongly positive formol-gel test and a rapid sedimentation rate were the only indications that the rheumatic process was not quiescent. The Weltmann reaction was almost always normal or to the right, and the temperature and pulse rate were normal after the first week of hospitalization. In this case we believe that the rheumatic process was essentially one of proliferation, with little or no exudative activity. In our experience, when a child with a previous rheumatic lesion which has advanced to the point of fibrotic changes develops an exudative exacerbation, the Weltmann reaction is less likely to swing to the left, as compared to an exudative exacerbation in a rheumatic patient in whom there has been little or no scarring of rheumatic origin.

Some of our results would seem to indicate that the formol-gel reaction is more apt to be positive in those cases of rheumatic carditis in which there is prolonged productive activity. If this is true, it would be in keeping with the opinion of Bing[3] who felt that hyperglobulinemia sufficient to cause a positive formol-gel reaction was encountered chiefly in the presence of "chronic inflammation."

The sedimentation rate, Weltmann reaction, and formol-gel test are all nonspecific tests. They merely reflect certain humoral changes, possibly qualitative and/or quantitative changes in the serum proteins occurring

concomitantly with a pathologic process. In rheumatic fever, the formol-gel test, in our hands, has been the least sensitive of these tests, the corrected sedimentation rate the most sensitive, and the Weltmann reaction intermediate in sensitivity.

As shown in Table II, there was no correlation between the Weltmann reaction and the formol-gel test. This is to be expected since a positive formol-gel test depends on the presence of a hyperglobulinemia, while, as shown by Carrière, Martin and Dufossé[30] and ourselves,[31] the Weltmann reaction has no direct relation to the globulin content of the serum.

As has been pointed out elsewhere,[22] the Weltmann reaction has a unique value in the study of rheumatic fever of childhood. It often enables us to classify the pathologic phase of the rheumatic process, whether it is exudative or productive, and whether one of these processes overbalances the other or whether they are in equilibrium. As a corollary, together with other laboratory data and the clinical state of the patient, it helps us to decide whether the rheumatic infection is in the active or convalescent phase. In Fig. 9 we have noted the possible state of the rheumatic process when various values for the sedimentation rate and Weltmann reaction are correlated. This of course has to take into account the clinical condition when it is applied to a particular patient.

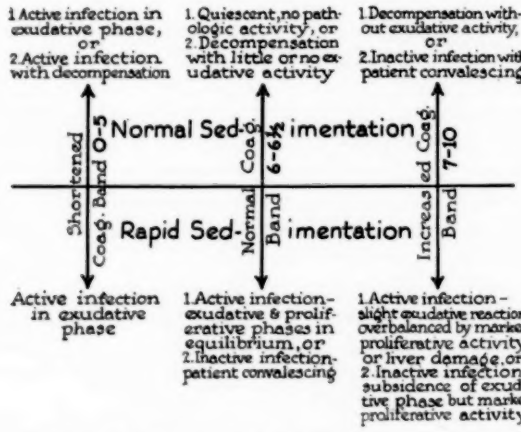
1. Active infection in exudative phase, or 2. Active infection with decompensation
1. Quiescent, no pathologic activity, or 2. Decompensation with little or no exudative activity
1. Decompensation without exudative activity, or 2. Inactive infection with patient convalescing
Normal Sedimentation
Shortened Coag. Band
0-5
Coag.
6-6½
Increased Coag. Band
7-10
Rapid Sedimentation
Active infection in exudative phase
1. Active infection - exudative & proliferative phases in equilibrium, or 2. Inactive infection - patient convalescing
1. Active infection - slight exudative reaction overbalanced by marked proliferative activity or liver damage, or 2. Inactive infection - subsidence of exudative phase but marked proliferative activity

Fig. 9.—Interpretation of Weltmann and sedimentation reactions in rheumatic heart disease.

We should like to emphasize again that rheumatic fever is not a disease in which there is an orderly sequence of events, so that the clinical interpretation of the underlying pathology is often difficult. Like tuberculosis, rheumatic fever is frequently characterized by exudative, active, necrotizing processes in one part of the organ involved, and proliferative, healing processes in another part. Another factor which

complicates further the picture in rheumatic fever is cardiac decompensation. It is the consensus that decompensation on a rheumatic basis in children is usually associated with the exudative phenomena of acute infection, although under the influence of decompensation, the sedimentation rate tends to slow and the Weltmann reaction tends to swing to the right. If, however, the sedimentation rate is corrected in relation to the red cell volume, the corrected sedimentation rate will often be increased, whereas the observed sedimentation rate may be normal or only slightly increased. In our group of eleven children with decompensation, eight had increased corrected sedimentation rates.

Finally, in speaking of the formol-gel reaction, Schultz and Rose were of the opinion that "in some instances this test appears to be a more delicate index of continued rheumatic activity than acceleration of the sedimentation rate because positive reactions may be obtained after the sedimentation rate has returned to normal levels." We do not agree with this for several reasons. First, an accelerated sedimentation rate per se is not necessarily an index of active rheumatic infection. We have pointed out previously[22] that the sedimentation rate may be increased during the convalescent proliferative phase of rheumatic fever to the same extent that it is in the active exudate phase. Second, it appears questionable to us whether some of the patients whom Schultz and Rose used to illustrate their opinion still had an active carditis when the sedimentation rate had returned to normal levels. Any nonspecific test such as the formol-gel test or even the sedimentation rate or Weltmann reaction must be interpreted and evaluated in consideration with the clinical findings, instead of the condition of the patient being interpreted in the light of such a nonspecific test. Third, although occasionally a child with clinically active rheumatic fever may have a normal or only slightly increased sedimentation rate, it is the consensus of numerous investigators[29] that in rheumatic fever the sedimentation rate is the last measurable factor to return to normal. The difficulty in the interpretation of the sedimentation rate in the convalescing rheumatic patient is not, as a rule, that of finding a slow rate in a case where the rheumatic process might still be active, but in finding a rapid rate when other laboratory tests and clinical findings indicate the cessation of rheumatic activity.

CONCLUSIONS

In a study of the formol-gel test, sedimentation rate, and Weltmann reaction during rheumatic fever of childhood, the formol-gel test was found to be the least sensitive index of the rheumatic state and the corrected sedimentation rate the most sensitive.

The Weltmann reaction is intermediate in sensitivity but gives unique information in that it helps to indicate the pathologic state of the rheumatic process, whether exudative or proliferative.

In severe rheumatic carditis the sedimentation rate is usually rapid and the Weltmann reaction gives a shift to the left, but the formol-gel test is frequently negative.

The formol-gel test is of little value in the study of rheumatic fever of childhood, because positive results are frequently obtained in the absence of carditis and negative results are obtained when carditis is obviously present.

A combined study of the corrected sedimentation rate and Weltmann reaction in rheumatic fever, when correlated with clinical observations, is of value in determining the state of the rheumatic process.

Nonspecific laboratory tests must be interpreted in the light of the clinical findings; the clinical state should not be evaluated on the basis of nonspecific tests alone.

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THE FIBRINOLYSIN TEST IN RHEUMATIC FEVER

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DURING a clinical study[1] with pediatric material it was observed that the semiweekly variations in the streptococcal fibrinolysin test of Tillett and Garner[2] followed certain definite trends, some of which appeared to have especial significance. Thus, frequently in rheumatic fever and in hemorrhagic nephritis, for week after week, the patient's plasma clot was found to resist lysis by cultures of human hemolytic streptococci. In an experience of four years there have been exceptions, but the frequency of this finding has been noteworthy. Other investigators[3-10] have reported a high incidence (an average of 80 per cent) of resistant clots in rheumatic fever. These observations have suggested to us the diagnostic use of the test, and our findings will be presented here in an attempt to evaluate the fibrinolysin test as a diagnostic aid in rheumatic infection.

METHODS OF STUDY

The fibrinolysin test has been used in the clinic for four years and three years ago was added to the routine laboratory examinations of children with rheumatic fever who were treated on the wards of the New Haven Hospital. Along with a total and differential white blood cell count, sedimentation rate determination, and culture of the nose and throat, the test was done at the time of the patient's admission and at weekly intervals during the period of hospitalization unless a change in the course of the disease indicated more frequent examinations. The clinical material for this report consisted of the children who were admitted early in the rheumatic attack and who were studied throughout their illness and convalescence, together with those dispensary patients whom we were able to follow in a similar manner.

Two criteria for the presence of active rheumatic fever were used. These were hot, swollen joints or active heart disease. The latter was identified by cardiac enlargement and a loud mitral murmur in a previously normal heart, or increasing cardiac enlargement and accentuation of the murmur, or a new murmur in a previously damaged heart. Either of these two objective signs, arthritis or carditis, in the absence of other demonstrable cause, was considered diagnostic in view of the age group of the patients. Rheumatic chorea, nodules, and pericarditis, when present, furnished corroborative evidence.

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FIBRINOLYSIN TEST

The method is that of Tillett and Garner[2] and has been described in detail in a preceding publication.[1] Two-tenths cubic centimeter of the patient's plasma, obtained by the centrifugation of oxalated blood, was placed in a small glass tube and diluted with 0.8 c.c. of normal salt solution. To this was added 0.5 c.c. of an eighteen-hour culture of hemolytic streptococcus (known to dissolve normal plasma clots in fifteen minutes or less) and 0.25 c.c. of calcium chloride (0.25 per cent solution). The contents of the tube were thoroughly mixed and incubated in a water bath at 37.5° C. A solid clot formed in about ten minutes. The interval between the time of clotting and that of complete liquefaction determined the result of the test: 4+, no lysis of the plasma clot in twenty-four hours; 3+, complete lysis in eight to twenty-four hours; 2+, complete lysis in three to eight hours; 1+, complete lysis in one to three hours; −, complete lysis in less than one hour. The clot was not shaken during the test; readings were made by tilting the tube. Tests were done within forty-eight hours of the collection of the blood, generally within twenty-four hours. The same strain of hemolytic streptococcus, Ro, was used for all the tests. This strain maintained its lytic activity, and duplicate tests from time to time using other active human strains gave similar results.

RESULTS

This report represents the results of the fibrinolysin test in seventy-six children with acute rheumatic fever. About 1,000 tests were done. The patients were from 4 to 15 years of age. All were followed from within one week of the onset of symptoms.

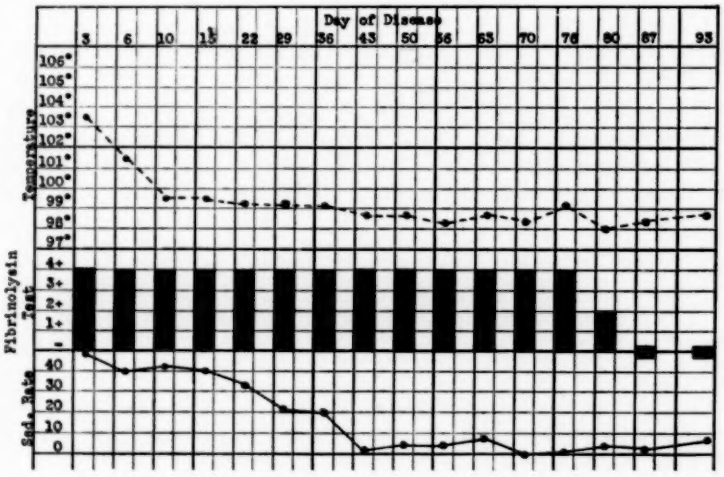

Chart 1.—Patient C. F., aged 14 years. Diagnosis: Acute rheumatic fever. The child was admitted on the third day of the disease, with fever and polyarthritis. The left elbow and both knees were red, swollen, and painful. The heart was not enlarged, and no murmur was heard. There was prompt subsidence of the arthritis with salicylate therapy and a more gradual disappearance of fever. On the sixth day of the disease, the electrocardiogram indicated active myocarditis with complete A-V block and abnormal S-T features. By the eleventh day the heart block had disappeared. The sedimentation rate remained elevated until the forty-third day. The child was discharged home on the fiftieth day, to be observed subsequently in the dispensary. No cardiac murmur developed.

Chart 1 summarizes the clinical course of a 14-year-old girl with acute rheumatic fever. In this patient completely resistant clots (4+ tests) persisted from early in the illness through convalescence. These were the results obtained in the majority of the patients in whom the test was positive. In some, the tests remained at a 3+ level or varied between a 3+ and 4+ until the time of decrescence. Two types of exception were noted in a total of three patients. One was the delayed appearance of positive tests in a child with arthritis and carditis developing during the course of scarlet fever. In this patient the test did not become positive until two weeks after these signs were manifest. In two patients the tests which had been persistently positive became negative for a few days and then returned to positive again, to remain so for the rest of the illness. The significance of this change is not clear. Both children were more ill when the tests were negative and one of them developed a transient recurrent arthritis. Both had large numbers of hemolytic streptococci in nasal and pharyngeal cultures taken at the time.

TABLE I

FIBRINOLYSIN TESTS IN ACUTE RHEUMATIC FEVER

TYPE OF PATIENT	NUMBER OF PATIENTS	POSITIVE TEST	NEGATIVE TEST
Ward	60	54	6
Dispensary	16	14	2
Total	76	68	8

The results of the test in the seventy-six children are summarized in Table I. Sixty were ward patients, and the remaining sixteen were treated in the dispensary. Although the group in which a patient was placed was not entirely dependent on the severity of the illness, by and large this was true. The dispensary patients were ambulatory and often sought medical treatment because they were "run down" or because of a painful, swollen joint presumably as a result of trauma. On the contrary the ward patients usually had more marked general symptoms and severe heart disease either wholly attributable to the immediate rheumatic attack or due in part to previous heart damage. The tests were positive in fifty-four of the sixty ward patients (90 per cent), and in fourteen of the sixteen dispensary patients (87.5 per cent). In the eight patients (11 per cent) in whom the test was negative, it remained so for weeks. The only apparent difference between this group and the group giving a positive test was a slightly lower incidence of heart disease.

The number of the rheumatic attack did not seem to influence the test, as is shown in Table II. Patients in whom there was no history of previous rheumatic fever and who were known to have normal hearts prior to the rheumatic attack under study were considered to be ill with

a first attack of rheumatic fever. Patients in a second attack had been treated at this hospital during a previous attack or were known to have mitral stenosis. Comparable criteria were used for patients in a third and fourth attack. Tests were positive in thirty-seven of the forty-two patients (88 per cent) in a first attack, and in twenty-five of twenty-eight patients (82 per cent) during a second attack. The number of patients observed in third and fourth attacks, five and one, respectively, is too small to yield significant results. However, the presence of positive tests in all of the six patients would seem to support the view that the test is as frequently positive in the recurrent attacks of rheumatic fever. Although it is not shown in Table II, since patients were included only once, one child was observed during two attacks and another in three attacks of rheumatic fever. Tests were positive in all five attacks in these two patients. To date, none of the patients in whom the test was negative has been observed in a subsequent attack.

TABLE II

FIBRINOLYSIN TESTS IN FIRST AND SUBSEQUENT ATTACKS OF RHEUMATIC FEVER

ACUTE RHEUMATIC FEVER	NUMBER OF PATIENTS	FIBRINOLYSIN TESTS	
		POSITIVE	NEGATIVE
First attack	42	37	5
Second attack	28	25	3
Third attack	5	5	0
Fourth attack	1	1	0

TABLE III

FIBRINOLYSIN TESTS IN FIRST ATTACK OF ACUTE RHEUMATIC FEVER, RELATED TO PRESENCE OR ABSENCE OF RHEUMATIC HEART DISEASE

ACTIVE HEART DISEASE	NUMBER OF PATIENTS	FIBRINOLYSIN TESTS	
		POSITIVE	NEGATIVE
Absent	9	6	3
Probably present	7	6	1
Present	26	25	1

There is a suggestion that positive tests are found more regularly in the severely ill patients. Table III shows the results of the test in relation to the presence of active heart disease in forty-two children in a first attack of rheumatic fever. Tests were also positive in all of seven patients who died during the active infection. These observations are in accord with those of Waaler,[9] who found that the resistance of the plasma clot varied directly with the severity of the disease. On the contrary, Perry[10] was unable to correlate the clinical course with the results of the test, while Stuart-Harris[7] felt that patients with positive tests (resistant clots) usually did better.

The value of the test as an index of rheumatic activity is also not clear. In the experience of Stuart-Harris,[7] the test remained positive after the erythrocyte sedimentation rate had returned to normal. According to

Perry,[10] the test bears no strong relationship to the sedimentation rate. In this series, the positive tests generally persisted for a period of several weeks after the sedimentation rate had returned to normal, although in some of the chronic cases the test became negative while the sedimentation rate remained elevated.

DISCUSSION

The behavior of the test adds something to the evidence that hemolytic streptococci are of etiological significance in rheumatic fever. Another test related to hemolytic streptococci, the antistreptolysin test, bears a relationship to rheumatic infection similar to that of the fibrinolysin test. Coburn and Pauli[11] found continued high antistreptolysin titers for months in rheumatic fever. Thus, a striking similarity exists in the length of time for which the two tests are positive.

The results suggest that the fibrinolysin test should be of aid in the diagnosis of rheumatic fever. The test was positive in the large majority of these patients as they came to the hospital for treatment, and these positive tests persisted for a long enough period of time to be helpful. The test is cheap, simple, and highly consistent. It appears to be nonspecific, but much of any resulting confusion can be avoided by interpreting the test in the light of the attendant circumstances.

In hospital practice the conditions which give rise to resistant clots (positive tests) and which might be confused with rheumatic fever are the severe acute infections such as pneumonia, sepsis, and typhoid fever. In most cases, the diagnosis of these diseases will be made by the development of their own characteristic signs, and with the beginning of convalescence, the fibrinolysin test will become negative. This is unlike the course of the test in rheumatic fever where positive tests persist for week after week, even after the fever has defervesced.

In dispensary practice there are few conditions other than rheumatic fever, hemorrhagic nephritis, and streptococcal cervical adenitis which give rise to a positive test. Accordingly, in ambulatory patients a positive test is of special significance because its specificity has been greatly enhanced by clinical circumstances.

SUMMARY AND CONCLUSIONS

The results of the fibrinolysin test in seventy-six children with rheumatic fever are reported.

In rheumatic fever the fibrinolysin test has diagnostic value when interpreted in the light of the other clinical findings.

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THE ELECTROCARDIOGRAM IN RHEUMATIC FEVER

A Study of Sydenham's Chorea

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A REVIEW was made of all cases of Sydenham's chorea admitted to the Children's Medical Service of Bellevue Hospital, from May, 1930, through September, 1938, in an effort to determine what possible aid the electrocardiogram might give in the diagnosis of rheumatic cardiac complication. This study is limited to the electrocardiographic changes which occurred following an attack of chorea, believed by most authorities to be a form of rheumatic fever.

During this period, 250 cases of chorea were admitted to the hospital. Sixty-nine of these were discarded because of a previous history of some other form of rheumatic fever. Any patient who developed a complication of rheumatic fever other than a carditis was also eliminated. Among those eliminated were a number with so-called "growing pains." Of the remaining 181 cases, sixty-one were males and 120, females, a ratio of 1:2, which coincides with the findings of others.[1] The age range was 5 to 14 years, with an average age of 9.1 years. Seventy-eight cases had a total of two to seven admissions to the hospital because of recurring attacks of chorea, but only those admissions during which electrocardiograms were taken were included in this series. The series as studied, therefore, consisted of 181 cases who were in the hospital 250 times with attacks of chorea. Each of these admissions was treated as an individual case for statistical purposes. A total of 314 electrocardiograms was taken; this forms the basis of the study.

NORMAL STANDARDS

Measurements of the heart rate and P-R and Q-T intervals were made in Lead II. The standards as given by the New York Heart Association[2] for P, QRS, and T waves were used as the normals in this series. Ashman and Hull,[3] and Hafkesbring, Drawe, and Ashman[4] found that, in the presence of normal rhythm, the P wave in Leads I and II is upright. In a series of 222 normal children, Lincoln and Nicholson[5] report only one case in which the P wave in Lead II was not upright. Inverted or diphasic P waves in Lead III often occur normally. Ashman and Hull[3] found that only 4 to 5 per cent of their normals showed inverted or diphasic P_3, while Lincoln and Nicholson[5] found a similar condition in 10 per cent of their normal cases.

An early abnormal electrocardiographic finding in rheumatic heart disease is the prolongation of the P-R interval. Formerly, 0.20 sec.

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was considered to be the upper limit of normal. This figure has been revised, since it is now recognized that one must correct both for age and heart rate. Hafkesbring, Drawe, and Ashman[4] found the P-R interval to range from 0.10 to 0.165 sec. in 100 normal children. In their series, only one P-R interval reached this upper limit, and that occurred in a patient whose heart rate was 57 beats per minute. Ashman and Hull[3] compiled a table based on a series of normal children, correcting the P-R interval for both age and heart rate. Their table was used as the normal standards for this series.

Hafkesbring, Drawe, and Ashman[4] found the width of the QRS deflections to vary from 0.05 to 0.09 sec., and in only two cases did it reach the highest level. Lincoln and Nicholson[5] obtained a range of 0.04 to 0.08 sec. Ashman and Hull consider over 0.09 sec. to be abnormal. Slurring of the QRS deflections was considered to be abnormal only if present in all three leads in the absence of low voltage.

Inversion of the T wave in Leads I and II in normal individuals is a rare occurrence.[3] The T wave in Lead III was inverted in 25 per cent of the subjects in the Ashman and Hull series, in 35.5 per cent of the Lincoln and Nicholson's series, and in 38 per cent as determined by Hafkesbring, Drawe, and Ashman.

The Q-T interval, which defines the length of electrical systole, is measured from the beginning of the QRS deflections to the end of the T wave. Only recently has much attention been directed to this phase of the electrocardiogram. White[6] defines the normal limits of the Q-T interval as 0.45 sec. for a heart rate of 45 beats per minute, 0.35 sec. for a rate of 75, and 0.25 sec. for a rate of 120. Bazett[7] derived the formula of $Q\text{-}T = K \sqrt{c}$ after comparing the Q-T intervals of normal electrocardiograms with their cycle lengths. K is a constant, while c represents the cycle length of the electrocardiogram in seconds. The Q-T interval is said to be prolonged if K exceeds 0.392 sec. in men, and 0.44 sec. in women. No figures for K in children are available. Ashman and Hull[3] derived the formula $Q\text{-}T = K \times \text{Log } 10\ (c + k)$, in which c represents the cycle length, and K and k are constants. From this formula, they worked out a table showing the upper limits of normal for the Q-T interval in children, men, and women. In their group of eighty-two normal children, all of the Q-T intervals came within the above limits. After examining more records of children and adults, Ashman[8] found this table to be satisfactory. The normals thus obtained by Ashman and Hull, were used as the standards in the Bellevue series. These normals are high when compared to those obtained from Bazett's formula.

The electrical axis was determined by the method of Dieuaide.[9] Thus, more than plus 90 degrees would indicate right axis deviation, and less than plus 30 degrees, left axis deviation.

METHOD OF ANALYSIS

For purposes of analysis, this series was divided into three groups. Group I consists of patients with chorea only, in whom no cardiac involvement was detectable by clinical or laboratory tests aside from the electrocardiogram. The electrocardiogram was taken while signs and symptoms of chorea were still present. Group II differs from Group I in that the electrocardiogram was taken after all signs or symptoms of chorea had disappeared. Group III consists of all cases in which a rheumatic cardiac diagnosis was made clinically, or by laboratory tests other than the electrocardiogram. The laboratory tests included temperature and pulse records, blood counts, sedimentation rates, and teleoroentgenograms. Four cases with active chorea were diagnosed as having cardiac involvement, only on abnormal electrocardiographic records. These were placed in Group I. If more than one electrocardiogram was taken during the same admission to the hospital, the one which showed some abnormality was chosen. Several patients, admitted to the hospital with repeated attacks of chorea, were studied in more than one grouping, depending upon the above conditions.

TABLE I

	FIRST ATTACK	REPEATED ATTACKS	TOTAL NO.	PERCENTAGE
Number	68	60	128	100
Average age	8.7	9.6		
Sex, male	25	21	46	35.9
female	43	39	82	64.0
Electrocardiogram				
Sinus tachycardia	19	12	31	24.2
Sinus arrythmia	49	43	92	71.8
Sinus bradycardia	1	0	1	0.7
Auriculoventricular nodal rhythm	1	0	1	0.7
P waves, high voltage	1	0	1	0.7
P waves, unusually notched	1	1	2	1.5
P_2, inverted or diphasic	12	11	23	17.9
P-R interval, prolonged	2	7	9	7.0
QRS waves, slurred	1	0	1	0.7
QRS interval, wide	2	0	2	1.5
T waves, high voltage	6	2	8	6.2
T waves, low voltage	0	1	1	0.7
T_2, inverted	30	29	59	46.1
Q-T interval, prolonged	9	12	21	16.4
Left deviation of electrical axis	9	9	18	14.0
Right deviation of electrical axis	5	2	7	5.4

Group I.—A statistical analysis of this group may be seen in Table I. The more important abnormalities of the electrocardiogram noted, were prolongations of the P-R and Q-T intervals and deviations of the electrical axis. Only one case showed an abnormal rhythm, namely, an auriculoventricular nodal rhythm.

Prolongation of the P-R interval was present in nine cases (7 per cent). Four cases in this group showed changing P-R intervals in subse-

quent electrocardiograms. This consisted of a decrease or increase of the interval by 0.03 to 0.06 sec. In each case the heart rates varied less than fifteen beats per minute. In addition to this abnormality of a changing P-R interval, all four cases had at least one electrocardiogram which showed a prolonged P-R interval.

Prolongation of the Q-T interval was present in twenty-one cases (16.4 per cent). Eleven of these (54 per cent), showed other abnormalities in the electrocardiogram. These abnormalities included five cases with prolonged P-R intervals, one case with large P waves, one with slurring of the QRS deflections in all three leads, one with widening of the QRS interval, five with left deviation of the electrical axis, and two with right deviation of the electrical axis, of which one was plus 120 degrees. Several of these cases had more than one abnormality, aside from the prolonged Q-T interval. Five cases with prolonged Q-T intervals had follow-up electrocardiograms. In all of them, the Q-T interval returned to normal. One of these five cases also had a prolonged P-R interval which became normal in the follow-up electrocardiogram.

The electrical axis ranged from minus 30 to plus 120 degrees. Eighteen cases (14 per cent) showed deviaton of the electrical axis to the left. A slight axis deviation to the left, ranging from plus 2 to 26 degrees, was present in fourteen cases. Three cases showed a definite left axis deviation, ranging from 0 to minus 10 degrees, and one case showed a marked left axis deviation of minus 30 degrees. Two of the four cases with definite or marked left axis deviation have been described above, one having prolonged P-R and Q-T intervals, the other having only the latter.

Seven cases (5.4 per cent) showed a deviation of the electrical axis to the right. Only one case showed more than a mild deviation to the right, having plus 120 degrees. This case has been described above as having a prolonged Q-T interval and large P waves.

Group II.—This group consists of fifty-eight cases convalescing from an attack of chorea. No cardiac involvement was present clinically or in laboratory tests other than the electrocardiogram. A statistical analysis of this group is given in Table II.

As these cases were convalescing, the number of electrocardiographic abnormalities were few. Only one case showed a prolonged P-R interval. Five cases showed prolonged Q-T intervals. Three of these showed other abnormalities, which included one case with isoelectric T waves in Lead II and inverted T waves in Lead III, and one case with diphasic T waves in Lead II and inverted T waves in Lead III. None of the five cases had a follow-up electrocardiogram.

Deviation of the electrical axis was present in twelve cases, of which eleven showed only a slight deviation to the left. One case showed a

slight deviation to the right, and in addition, had high T waves. The cases with slight left axis deviation showed no other significant changes in the electrocardiogram.

TABLE II

	FIRST ATTACK	REPEATED ATTACKS	TOTAL NO.	PERCENTAGE
Number	25	33	58	100
Average age	9.7	9.7		
Sex, male	7	11	18	31.0
female	18	22	40	68.9
Electrocardiogram				
Sinus tachycardia	6	5	11	18.9
Sinus arrythmia	16	22	38	65.5
Sinus bradycardia	0	2	2	3.4
Auriculoventricular nodal rhythm	0	0	0	0
P waves, high voltage	1	0	1	1.7
P waves, unusually notched	0	1	1	1.7
P_2, inverted or diphasic	3	9	12	20.7
P-R interval, prolonged	1	0	1	1.7
QRS waves, slurred	0	0	0	0
QRS interval, wide	1	0	1	1.7
T waves, high voltage	0	1	1	1.7
T waves, low voltage	0	0	0	0
T_2, inverted	14	18	32	55.1
Q-T interval, prolonged	3	2	5	8.6
Left deviation of electrical axis	4	7	11	18.9
Right deviation of electrical axis	0	1	1	1.7

TABLE III

	ACTIVE HEART DISEASE	INACTIVE HEART DISEASE	TOTAL NO.	PERCENTAGE
Number	36	28	64	100
Average age	8.46	9.40		
Sex, male	11	15	26	40.6
female	25	13	38	59.3
Electrocardiogram				
Sinus arrythmia	10	17	27	42.1
Sinus tachycardia	20	7	27	42.1
Sinus bradycardia	0	0	0	0
Auriculoventricular nodal rhythm	0	1	1	1.5
P waves, high voltage	1	1	2	3.1
P_2, inverted or diphasic	11	10	21	32.8
P waves, unusually notched	1	2	3	4.6
P-R interval, prolonged	11	3	14	21.8
QRS waves, unusually slurred	1	1	2	3.1
QRS interval, wide	0	0	0	0
T waves, high voltage	0	3	3	4.6
T waves, low voltage	0	0	0	0
T_2, inverted	10	10	20	31.2
Q-T interval, prolonged	12	7	19	29.6
Left deviation of electrical axis	9	4	13	20.3
Right deviation of electrical axis	3	3	6	9.3

Group III.—This group consisted of sixty-four cases on whom a cardiac diagnosis of active or inactive rheumatic heart disease was made clinically or by laboratory tests other than the electrocardiogram. The results are shown in Table III.

Abnormal rhythms were present in three cases. One case showed an auriculoventricular nodal rhythm. Another had a regular sino-auricular block every seventh beat, and the third had a 2:1 heart block which later disappeared during convalescence. Only the last two cases warranted a diagnosis of active rheumatic carditis.

Prolonged P-R intervals were present in fourteen cases (21.8 per cent). Eight of these were diagnosed clinically as having active carditis.

In this group, follow-up electrocardiograms were taken in thirteen cases, of which ten were considered to have active rheumatic heart disease. These electrocardiograms were usually repeated because of the presence clinically of active carditis, or because of an abnormal finding in the first electrocardiogram. In the follow-up electrocardiograms, seven cases with prolonged P-R intervals and active carditis, showed a decreased time interval varying from 0.03 to 0.09 sec. One patient with active carditis and prolonged P-R intervals showed no changes in the interval in a later electrocardiogram. One patient with inactive heart disease showed a P-R interval of 0.13 sec., with a heart rate of 60 beats per minute. This case later developed a longer interval of 0.16 sec. with a faster rate of 94 per minute, indicating some cardiac activity. One patient with inactive and three with active heart disease had normal P-R intervals and showed no changes in subsequent electrocardiograms.

Prolongation of the Q-T interval was present in nineteen cases (29.6 per cent). Twelve of these (63.1 per cent), showed other abnormalities in the electrocardiogram. These included ten cases with prolonged P-R intervals, two with high T waves, and two with definite left axis deviation. Six cases, all of which showed prolonged Q-T and P-R intervals, had follow-up electrocardiograms. Three of these showed a return to normal of both time intervals. In a fourth case, the P-R interval remained prolonged, while the Q-T interval returned to normal. The fifth showed the Q-T interval remaining prolonged, while the P-R interval returned to normal. The last case, with a follow-up electrocardiogram, showed that both the Q-T and P-R intervals remained prolonged.

The electrical axis ranged from minus 15 to plus 108 degrees. Thirteen cases (20.3 per cent) showed a deviation of the electrical axis to the left. A slight deviation to the left, ranging from plus 4 to 20 degrees, was present in eleven cases. Two cases, both with active carditis, showed a definite left deviation of the electrical axis, with minus 10 and 15 degrees. Both of these showed prolonged P-R and Q-T intervals. Six cases showed slight deviation of the electrical axis to the right, ranging from plus 95 to 108 degrees. One of these was the case with auriculoventricular nodal rhythm, while another had a prolonged P-R interval.

COMMENT

In this series of cases which was limited to those patients whose first sign of rheumatic fever was chorea, numerous abnormalities in the

electrocardiograms were noted. In Groups I and II no evidence of cardiac involvement was present clinically or in other laboratory procedures. Despite this, abnormalities in the electrocardiogram were noted in 42.1 per cent of Group I, and in 32.7 per cent of Group II, or a total of 39 per cent of both groups. However, one-third of the electrocardiographic abnormalities in Group I and one-half in Group II were the presence of a deviation of the electrical axis only. These figures do not include any changes in the P or T waves in Lead III, or the presence of sinus arrythmia, sinus tachycardia, or sinus bradycardia. Similarly, it was found that 63.9 per cent of the cases in Group III, showed some abnormality in the electrocardiogram. Deviations of the electrical axis only were found in but one-fifth of these. Thus, the electrocardiogram in Group III served to corroborate the cardiac diagnosis and in many cases helped to decide the presence of active rheumatic carditis.

Not all of the electrocardiographic changes were important enough by themselves to warrant a cardiac diagnosis. These consisted of changes in rhythm, slight deviations of the electrical axis, and abnormalities in the P, QRS, and T waves. However, when these were interpreted in the light of clinical or other laboratory findings, they assumed greater importance. Thus a wide, high, or notched P wave, in the presence of clinical mitral valvulitis, might indicate auricular pathology. Frequently, as noted above, two or more abnormalities were present in the same electrocardiogram. When this occurred, a diagnosis was more likely to be made.

Inversion of the P or T waves in Lead III occurred more frequently than in the normal series of Ashman and Hull,[3] Hafkesbring, Drawe, and Ashman,[4] and Lincoln and Nicholson,[5] as mentioned above. The occurrence of an inverted P or T wave in Lead III in an electrocardiogram by itself is of little aid in a diagnosis of a cardiac involvement.

Two of the more significant phases of the electrocardiogram are the P-R and Q-T intervals. Prolongation of the P-R interval in children has been accepted as a sign of active carditis. Not enough investigation of prolonged Q-T intervals has been done as yet to warrant a similar diagnosis of active carditis. In this series of cases, Ashman and Hull's normal standards were used to determine prolongation of the Q-T interval. Forty-five patients, fifteen boys and thirty girls, were thus found to have prolonged Q-T intervals. In using Bazett's formula, as mentioned above, with his normal standards as given for men and women, eighty-four patients had prolonged Q-T intervals. Of these, sixty-eight were boys and only sixteen were girls. This high figure for boys is due to the fact that Bazett's normal standards for men are lower than for women. As previously stated, he does not give any normals for children.

Since Ashman and Hull's standards were used in this series, forty-five cases were found to have prolonged Q-T intervals (Table IV). This was compared to only twenty-four cases with prolonged P-R intervals. Twenty-six cases of the former and ten of the latter occurred in the

TABLE IV

	GROUP I	GROUP II	GROUP III	TOTAL	PERCENTAGE
Prolongation of P-R interval	9	1	14	24	9.6
Prolongation of Q-T interval	21	5	19	45	18.0
Prolongation of both P-R and Q-T intervals	5	1	10	16	8.0

absence of a diagnosis of heart disease (Groups I and II). Only eight cases with prolonged P-R intervals did not show prolonged Q-T intervals. Thus it can be seen that there was a high degree of correlation of prolonged Q-T interval with prolonged P-R interval. It should be noticed that the occurrence of prolonged Q-T interval was almost twice that of prolonged P-R interval. Therefore, it seems logical to attribute greater significance to the Q-T interval than has been done heretofore.

SUMMARY

The electrocardiograms of 181 patients, in whom Sydenham's chorea was the first sign of rheumatic fever, were studied. These patients were admitted to the hospital 250 times.

Abnormalities were noted in 39 per cent of the electrocardiograms in the absence of clinical or other laboratory findings of cardiac involvement.

The more significant of these abnormalities was the prolongation of the P-R and Q-T intervals. The latter occurred in 18 per cent of the series as compared to only 9.6 per cent of the former. Prolongation of both time intervals occurred in 8 per cent of the series.

The electrocardiogram may corroborate a clinical diagnosis of rheumatic cardiac involvement and show the presence of active carditis.

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THE HIPPURIC ACID LIVER FUNCTION TEST IN CHILDREN

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THE multiplicity of physiologic functions of the liver has led to the development of many different liver function tests, some of which have been applied to children. In recent years the hippuric acid test, introduced by Quick[1] in 1933, has been found to be a valuable method. This test is based on the response of the liver to benzoic acid, administered as sodium benzoate. When sodium benzoate is ingested, the benzoic acid radical is conjugated with glycine in the liver to form hippuric acid, which is excreted through the kidneys. Two mechanisms are brought into play: (1) the liver furnishes the required amount of glycine; and (2) it conjugates the glycine with benzoic acid. Quick and other observers have demonstrated that the capacity of the liver to synthesize the hippuric acid is diminished in disease of the liver.

The method as described by Quick consists of giving the subject 6 Gm. of sodium benzoate, after which four hourly urine specimens are collected. The excreted hippuric acid is then determined quantitatively by means of a simple analytic method. Weichselbaum and Probstein[2] have increased the accuracy of the laboratory procedure without impairing its simplicity. Probstein and Londe,[3] using the improved technique, obtained higher normal values for the excretion of hippuric acid during the test than those given by Quick. In addition, they demonstrated that in healthy persons, 4 Gm. of sodium benzoate is sufficient to elicit a maximum of response from the liver during a four-hour period, this maximum rate of elimination being reached during the second hour of the test. In view of these findings, 4 Gm. of sodium benzoate was established as the standard dose. Normal persons ingesting 4 Gm. of sodium benzoate eliminate at least 50 per cent in the first two hours, and not less than 80 per cent in four hours. Deviations from the normal shape of the time curve of elimination, even though the total four-hour excretion be normal, are considered to be indicative of moderately disturbed hepatic function. According to Probstein and Londe, a satisfactory routine test can be run by collecting the urine for only two hours after the ingestion of the benzoate, and performing only one determination of hippuric acid. Elimination of not less than 50 per cent of the benzoate in two hours is considered to be normal.

To date, we have found two studies on the hippuric acid liver function test in children. Bollettino[4] examined forty-four children. He gave 0.1 Gm. of sodium benzoate per kilogram of body weight, using Quick's analytic method. Nine normal children eliminated 47 per cent in four hours, and twenty patients without clinical evidence of hepatic

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disease had outputs of from 43 to 73 per cent; fifteen patients with clinical signs of hepatic disease excreted from 8 to 58 per cent. Bonduel[5] also used Quick's laboratory procedure and administered 4 Gm. sodium benzoate to children under 10 years of age, and 6 Gm. to older children. Although tests were performed on normal children, no figures are presented. He states that patients with definite hepatic disease eliminated diminished amounts of hippuric acid.

Bonduel catheterized his subjects when small volumes of urine were voided. He also performed urea clearance tests on all his patients in order to rule out renal retention of the hippuric acid. Snapper and Grünbaum[6] and Probstein and Londe[3] have shown, however, that only in the presence of severe renal function impairment associated with urea retention may the excretion of hippuric acid be affected. The last-named authors, therefore, merely ascertained the urea nitrogen in their work on adults.

Since both Bollettino and Bonduel used Quick's analytic method, their results are probably too low. We decided, therefore, to apply the test to children, using the improved technique described by Weichselbaum and Probstein. Two immediate problems to be solved were: (1) the quantity of sodium benzoate to be used; and (2) the definition of the normal range of variations in the elimination of hippuric acid. As to the dose to be used, we were governed by the necessity of employing a quantity of sodium benzoate capable of eliciting a maximum response from the liver. Smaller quantities, which do not tax the capacity of the normal liver, may be efficiently handled by the diseased liver too. Bearing in mind that the weight of the liver is from 3 to 4 per cent of the body weight during the greater part of childhood, as compared to from 2.5 to 3 per cent in adults,[7] and on the basis of preliminary tests, we decided to give 3 Gm. to children weighing less than 40 kg., and 4 Gm. to those above this weight. The adult of average size receives in our procedure about 0.06 Gm. per kilogram of body weight, while the children received from 0.074 to 0.19 Gm. per kilogram.

We would have preferred to perform the test on active healthy children for the establishment of normal values. However, this was unfortunately impossible, and we were forced to confine our studies to patients who showed no clinical signs of hepatic disease. In all, we examined sixty-three children ranging from 3 to 15 years of age as normal controls. For discussion these subjects are divided into three groups:

1. Fourteen children from the wards of the St. Louis Shriners' Hospital who were in the hospital for orthopedic treatment, who had no infections, and who were all up and active.

2. Thirty-four patients from the pediatrics service of the Jewish Hospital and from the medical service of the St. Louis Children's Hospital, suffering or recovering from various illnesses. None of them had any signs of hepatic disease and none were febrile when the tests were done.

3. Fifteen children who were admitted to the Jewish Hospital for tonsillectomy, because of recurrent severe upper respiratory infections. The hippuric acid tests were performed on the day previous to the operation.

In a fourth group we examined nine patients with clinical evidences of hepatic disease.

The preparation for the test was essentially the same as that outlined by Quick. A breakfast of tea and a piece of dry toast was given to the subject one hour before the sodium benzoate was administered. Following the ingestion of the drug, four hourly urine specimens were collected. Occasionally the subjects could not void every hour, so that some specimens were collected at the end of two-hour intervals. Vomiting from the nauseating effects of the drug occurred more frequently than in adults. For this reason, a small quantity of chocolate syrup sweetened with saccharine was added to the peppermint-flavored solution containing the sodium benzoate. This mixture was given cold.

The analytic procedure was carried out as follows: Measure the volume of the urine specimen. If it is above 150 c.c., add a few drops of glacial acetic acid and evaporate to a volume of 150 c.c. or less. Add 30 Gm. of sodium chloride per 100 c.c. of urine, and heat with shaking until the salt is dissolved. Cool the solution to about 15 to 20° C. by immersion of the flask in ice-cold water, add 1.2 c.c. of concentrated hydrochloric acid, and scratch the sides of the flask with a glass rod to enhance the crystallization of the hippuric acid. (This apparently trivial step is important.) Allow to stand for fifteen minutes in the cold water bath, then filter through a Hirsch funnel (diameter of perforated plate, 47 mm.), using moderate suction. Wash the precipitate with chilled 30 per cent sodium chloride solution from a wash bottle, using the washing fluid first to rinse the flask in which the precipitation has been performed. It is not necessary, however, to transfer the precipitate to the filter quantitatively. The precipitate is washed adequately when the washing fluid is free of concentrated hydrochloric acid. Transfer the funnel with its contents onto the flask that still contains some of the hippuric acid crystals, and rinse the filtered hippuric acid into it by dissolving it in hot water; to this end, use a fine-tipped wash bottle. All of the hippuric acid is now in the flask in which it had been precipitated; heat until all the hippuric acid particles adhering to the flask dissolve, and titrate while hot with 0.5 N sodium hydroxide, with phenolphthalein as an indicator.

The number of cubic centimeters of 0.5 N sodium hydroxide used for neutralization is multiplied by 0.072, which gives the amount of sodium benzoate in grams from which the hippuric acid was derived. If to this amount one adds the correction for the solubility of hippuric acid (0.123 Gm. per 100 c.c. of urine) in terms of sodium benzoate, i.e., 0.10 Gm. sodium benzoate, one obtains the sodium benzoate value of the specimen, with a maximum error of 10.5 mg. per 100 c.c.

Either bile or protein in the urine interferes with the procedure, but can be removed readily by the following method, recently suggested to us by Dr. Michael Somogyi: Add 5 c.c. of 30 per cent zinc sulfate and then 2.5 c.c. of 2.5 N sodium hydroxide per 100 c.c. of urine, shake, and filter. If the quantity of protein is very large, heat to near boiling temperature on a steam bath or by immersion in boiling water before filtering. For the rest, the procedure is the same as for normal urines, but for the fact that the urine is diluted with the precipitants and that only an aliquot portion is used for analysis. This must be taken into account in the calculation of the results.

TABLE I

HIPPURIC ACID TEST IN CHILDREN WITH ORTHOPEDIC CONDITIONS (CONTROL GROUP 1)

NO.	SEX	AGE (YR.)	HEIGHT (CM.)	IDEAL WEIGHT (KG.)	DIAGNOSIS	DOSE OF SODIUM BENZOATE (GM.)	HIPPURIC ACID EXCRETED									
							1ST HOUR		2ND HOUR		3RD HOUR		4TH HOUR		TOTAL	
							GM.	%	GM.	%	GM.	%	GM.	%	GM.	%
1	F	9	123	25	Poliomyelitis	3	0.58	19	0.63	21	0.74	24	0.28	9	2.23	75
2	F	8	125	25½	Clubfoot	3	0.46	15	0.62	21	0.67	22	0.47	16	2.22	74
3	F	8	125	25½	Poliomyelitis	3	0.55	18	0.60	20	0.62	21	0.47	16	2.24	75
4	F	8	125	25½	Poliomyelitis	3	0.59	20	0.72	24	0.64	21	0.41	14	2.36	79
5	M	14	125	26	Normal	3	0.70	23	0.91	30	0.66	22	0.20	7	2.47	82
6	F	9	130	29	Poliomyelitis	3	0.80	27	0.98	33	0.51	17	0.04	1	2.33	78
7	M	9	132	30	Poliomyelitis	3	0.32	11	0.68	23	0.82	27	0.32	10	2.14	71
8	M	10	135	32	Healed burn	3	0.58	19	1.02	34	0.80	27	0	0	2.40	80
9	M	10	138	33	Spastic monoplegia	3	0.36	12	0.95	32	0.55	18	0.16	5	2.02	67
10	F	12	143	38	Healed burn	3	0.89	30	0.71	23	0.72	24	0.09	3	2.41	80
11	M	14	152	45	Poliomyelitis	4	0.89	22	1.24	31	0.85	21	0.23	6	3.21	80
12	M	13	158	49	Healing fracture	4	1.40	35	0.75	19	0.32	8	0.29	7	2.76	69
13	F	13	160	53	Healed osteomyelitis	4	0.90	22	1.05	26	0.90	23	0.23	6	3.08	77
14	F	15	158	53	Poliomyelitis	4	0.82	20	1.00	25	0.83	21	0.22	6	2.87	72

As to the control of the renal factor in this test, we have already mentioned that hippuric acid may be retained only where impairment of renal function is severe enough to cause urea retention. Since we do not commonly have to contend in children with the degenerative vascular diseases seen in adults, and since severe renal insufficiency is rare in children without clinical signs or history of kidney disease, we did not deem it necessary to make routine blood urea nitrogen determinations.

RESULTS*

Group 1.—Considering the nature of this group, we think that the children in it can be considered normal for our purposes. Ten members of this group had ideal weights of from 25 to 38 kg. These received 3 Gm. of sodium benzoate, and, as may be seen in Table I, excreted from 67 to 82 per cent in four hours, with only one falling below 70 per cent. During the first two hours, the quantity eliminated varied from 34 to 60 per cent, the average being 45 per cent. As we observed in normal adult subjects, the maximum rate of excretion tends to occur during the second hour; in seven of nine cases the maximum was reached in the second hour.

Four children in this group, weighing over 40 kg., were given 4 Gm. of sodium benzoate. These subjects excreted from 69 to 80 per cent in four hours, with an average of 74 per cent. Elimination in the first two hours ranged from 45 to 53 per cent, with an average of 50 per cent. The maximum rate of excretion was reached during the second hour in three of the four subjects.

Group 2.—In this group, eighteen of the children whose ideal weights ranged from 21 to 39 kg. received 3 Gm. of sodium benzoate. Of these, fifteen excreted from 68 to 88 per cent in four hours, with an average of 79 per cent (Table II). Excretion during the first two hours in this group varied from 32 to 58 per cent, with an average of 47 per cent. The peak of elimination in nine of twelve cases was reached during the second hour. As may be seen, the rate of excretion, as well as the total elimination in four hours, is on the whole similar to that seen in Group 1.

In Group 2 there were eight patients with ideal weights of 40 kg. or over. These children were given 4 Gm. of sodium benzoate. Six of them eliminated from 79 to 92 per cent in four hours, with an average of 86 per cent. Excretion during the first two hours ranged from 41 to 74 per cent, the average being 53 per cent. The highest rate of elimination was attained during the second hour in four of the six subjects. These figures are somewhat higher than our findings in the larger children of Group 1, and approach the normal adult range.

In Group 2, Patients 4, 16, 19, 20, 24, 25, and 26, with ideal weights of less than 40 kg., all received 4 Gm. of sodium benzoate for the test dose.

*The quantities of hippuric acid excreted are given in sodium benzoate equivalents both in the tables and in the text.

The results in all of the tables, excepting Table V, are arranged in the order of the ideal weights (Baldwin-Wood) corresponding to height and age of the subjects. We have done this because the ideal weight in subjects very much underweight or overweight probably bears a closer relationship to the weight of the liver than does the actual weight. In Table I we give the ideal weights only, because the subjects were wearing casts.

TABLE II

HIPPURIC ACID TEST IN CHILDREN WITH MISCELLANEOUS CONDITIONS (CONTROL GROUP 2)

NO.	SEX	AGE (YR.)	HEIGHT (CM.)	ACTUAL WEIGHT (KG.)	IDEAL WEIGHT (KG.)	DIAGNOSIS, REMARKS	DOSE OF SODIUM BENZOATE (GM.)	HIPPURIC ACID EXCRETED									
								1ST HOUR		2ND HOUR		3RD HOUR		4TH HOUR		TOTAL	
								GM.	%	GM.	%	GM.	%	GM.	%	GM.	%
1	F	3	85	9½	12	Celiac disease	3	0.21	7	0.32	11	0.20	6	0.30	10	1.03	34
2	M	4	100	18	16	Rheumatic fever	3	0.40	13	0.48	16	0.53	18	0.58	19	1.99	66
3	M	4½	98	17	16	Wilms' tumor of kidney, nephrectomy	3	0.35	12			0.48*	16	0.52	17	1.35	45
4	F	6	108	15	19	Still's disease	4	0.42	10	0.74	19	0.48	12	0.74	19	2.38	60
5	M	7	113	20	21	Subsided upper respiratory infection	3	0.25	8	0.21	7	0.23	8	0.06	2	0.75	25
6	M	6	115	16	22	Asthma, malnutrition	3	0.42	14	0.55	18	0.66	22	0.41	14	2.04	68
7	M	8	118	25	23	Perthes' disease	3	0.63	21	0.74	25	0.68	23	0.23	8	2.28	76
8	M	12	117	?	23	Chronic arthritis	3	0.21	7	0.68	23	0.36	12	0	0	1.25	42
9	F	7	123	24	24	Subsided upper respiratory infection	3	0.36	12	0.52	17	0.52	17	0.41	14	1.81	60
10	F	7	123	25	24	Convalescent pneumonia	3	0.57	19	0.62	21	0.61	20	0.28	9	2.08	69
11	F	8	123	24	25	Sinusitis	3	0.47	16			1.43*	47	0.45	15	2.35	78
12	M	8	123	24	25	Sinusitis	3	0.86	29	0.86	29	0.74	25	0.11	3	2.57	86
13	M	8	125	21	26	Subsided catarrhal jaundice	3	0.63	21	0.85	28	0.80	27	0.29	10	2.57	86
14	M	7	128	25	26	Subsided catarrhal jaundice	3	0.71	24	0.88	29			0.86*	29	2.45	82
15	M	7	125	23	26	Recovered upper respiratory infection	3	0.45	15	0.55	18	0.66	22	0.55	19	2.21	74
16	M	10	132	25	30	Bronchiectasis	4	0.68	17	0.74	18	0.74	19	0.35	9	2.51	63
17	M	10	135	24	32	Chorea	3	0.72	24			1.74*	58	0.18	6	2.64	88
18	F	10	135	30	32	Recovered acute sinusitis	3	0.20	7	1.53	51	0.21	7	0.32	11	2.26	76

19	M	11	138	26	33	Chronic arthritis	4	0.66	16	0.91	23	0.63	16	0.13	3	2.33	58
20	F	12	138	40	34	Rheumatic heart disease	3	0.62	21	0.72	24	0.66	22	0.42	14	2.42	81
							4	0.72	18	0.72	18	0.76	19	0.62	16	2.82	71
21	M	14	140	29	35	Hypoglycemic attacks	3	0.73	24	0.78	26	0.72	24	0.16	5	2.39	79
22	M	9	143	28	36	Convalescent pneumonia	3			1.70*	57	0.62	21	0.29	9	2.61	87
23	M	11	143	30	37	Convalescent appendectomy	3	0.76	25	0.84	28	0.65	22	0.14	5	2.39	80
24	M	14	143	42	38	Rheumatic heart disease	4	0.67	17	0.98	24	0.98	24	0.38	10	3.01	75
25	M	13	145	37	39	Paronychia, nitrous oxide anesthesia on previous day	4	0.96	24	1.21	30	0.26	7	0	0	2.43	61
26	M	14	145	37	39	Rheumatic heart disease	3	0.50	17	1.06	35	0.54	18	0.23	8	2.33	78
							4	0.68	17	0.68	17	0.97	24	0.71	18	3.04	76
27	M	11	150	43	42	Convalescent mastoiditis, pneumococcus meningitis	4	0.74	18	0.90	23	1.05	26	0.68	17	3.37	84
28	M	14	150	48	43	Aniline dye poisoning	4	0.39	10	0.64	16	1.05	26	0.59	15	2.67	67
						Recovered	4	0.92	23	1.18	29	1.12	28	0.48	12	3.70	92
29	F	13	150	50	44	Rheumatic heart disease	3	0.95	32	1.23	41	0.37	12	0	0	2.55	85
							4	0.95	24	1.39	35	0.76	19	0.53	13	3.63	91
30	M	13	155	60	47	Healed infected laceration	4			1.79*	45	0.66	16			2.45	61†
31	M	14	155	44	47	Convalescent pneumonia	4	1.34	33	1.65	41	0.39	10	0	0	3.38	84
32	M	14	160	48	51	Rheumatic heart disease	3	0.97	32	0.81	27	0.55	19	0.21	7	2.54	85
							4	0.89	22	1.06	27	1.12	28	0.37	9	3.44	86
33	F	14	160	54	51	Rheumatic heart disease	4	0.68	17	1.14	29	0.76	19	0.57	14	3.15	79
34	F	10	165	59	54	Obesity, rheumatoid arthritis	4	0.39	10	0.64	16	0.63	16	0.56	14	2.22	56

*Excreted in this and preceding hour.
†Total for three hours only.

Patients 20 and 26 were also tested with 3-Gm. doses. If we examine the maximum hourly response to both doses by these two subjects, we find that on taking 4 Gm. of sodium benzoate, they eliminated virtually the same maximum quantity of hippuric acid in one hour as when they took 3 Gm. For all seven of the children receiving 4 Gm., the maximum response during a single hourly period varied from 0.74 to 1.21 Gm., the average being 0.90 Gm., while for the twelve patients of Group 2 receiving 3 Gm. (on the basis of their weights), the maximum excretion ranged from 0.66 to 1.53 Gm., with an average of 0.88 Gm.

On the basis of these findings we conclude that, under the standard conditions, 3 Gm. of sodium benzoate is sufficient to elicit an optimum response during one of the four hourly periods of the test in children whose ideal weight is less than 40 kg.

Two of the patients in Group 2, with ideal weights above 40 kg., received both doses of sodium benzoate. Patient 28 excreted an hourly maximum of 1.39 Gm. with 4 Gm., and 1.23 Gm. with 3 Gm., of sodium benzoate; Patient 31 eliminated an hourly maximum of 1.12 Gm. with the larger, and 0.97 Gm. with the smaller, quantity. Thus, it would seem that children with ideal weights above 40 kg. should be given the adult dose, i.e., 4 Gm. of sodium benzoate, in order to allow the liver to act at maximum capacity.

TABLE III

COMBINED RESULTS OF HIPPURIC ACID TESTS FROM CONTROL GROUPS 1 AND 2

NUMBER OF SUBJECTS	AGE	IDEAL WEIGHT	DOSE OF SODIUM BENZOATE	PERCENTAGE OF SODIUM BENZOATE EXCRETED IN FIRST TWO HOURS*			PERCENTAGE OF SODIUM BENZOATE EXCRETED IN FOUR HOURS		
				LOWEST	HIGHEST	AVERAGE	LOWEST	HIGHEST	AVERAGE
25	6 to 14 yr.	21 to 39 kg.	3 Gm.	32	58	46	67	88	79
10	11 to 15 yr.	42 to 54 kg.	4 Gm.	41	74	52	69	92	82

*Twenty-two subjects.

In Table III we have combined the ranges and averages of the normal results in Groups 1 and 2. Twenty-five children (fifteen boys and ten girls) receiving 3 Gm. of sodium benzoate eliminated from 67 to 88 per cent in four hours, with an average of 79 per cent. Only three of the children excreted less than 70 per cent. The boys tended to eliminate somewhat larger quantities, averaging 79 per cent as compared to 76 per cent for the girls.

We have results for the first two hours of the test in twenty-two of these children. The elimination during this period varied from 32 to 58 per cent, with an average of 46 per cent. In only five cases is the figure for this period lower than 40 per cent.

There were ten subjects (six boys and four girls) who gave normal results with the 4-Gm. dose in Groups 1 and 2. These children excreted from 69 to 92 per cent in four hours and averaged 82 per cent. The first two-hour eliminations varied from 41 to 74 per cent, only one falling below 45 per cent. The average is 56 per cent.

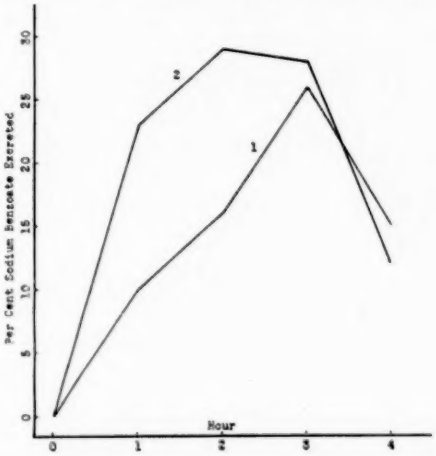

Fig. 1.—Patient 28, Table II. *1*, Impaired function due to aniline dye poisoning; *2*, normal function following recovery.

Using the criteria established above, we find in Group 2 two patients with chronic arthritis (8 and 33, Table II), and two patients (5 and 9, Table II) recovering from acute upper respiratory infections, in whom hippuric acid excretion was below normal. Patient 28 showed a definite disturbance caused by aniline dye poisoning. His four-hour total was 67 per cent, and the amount excreted during the first two hours was only 26 per cent. After his recovery, repetition of the test gave normal results (Fig. 1). Patient 2, a child with quiescent rheumatic fever, and with an ideal weight of 16 kg., was able to eliminate 66 per cent of a 3-Gm. dose in four hours and 47 per cent in three hours. On the other hand, Patient 3, whose ideal weight was also 16 kg. and who had recovered from a nephrectomy for Wilms' tumor of the right kidney, excreted only 45 per cent in four hours and 28 per cent in three hours. Since the renal factor is ruled out by normal blood nonprotein nitrogen, this result can be viewed as an index of disturbed liver function. We cannot make any comments on Patient 1, a case of celiac disease, since we have no comparative data. It is interesting to note that two of the children who had recovered from catarrhal icterus gave normal results.

Group 3.—This group of children (Table IV), referred to the hospital for tonsillectomy because of histories or evidences of repeated upper respiratory infections, was also examined for the purpose of obtaining

TABLE IV

HIPPURIC ACID TEST IN CHILDREN ADMITTED TO HOSPITAL FOR TONSILLECTOMY

NO.	SEX	AGE (YR.)	HEIGHT (CM.)	ACTUAL WEIGHT (KG.)	IDEAL WEIGHT (KG.)	DOSE OF SODIUM BENZOATE (GM.)	HIPPURIC ACID EXCRETED									
							1ST HOUR		2ND HOUR		3RD HOUR		4TH HOUR		TOTAL	
							GM.	%	GM.	%	GM.	%	GM.	%	GM.	%
1	F	3	98	17	15	3	0.28	9	0.79	27	0.30	10	0.04	1	1.41	47
2	M	3	98	15	16	3	0.14	5	0.28	9	0.57	19	0.10	3	1.09	36
3	F	4½	108	19	19	3	0.34	11	0.52	17	0.44	15	0.55	18	1.85	61
4	M	6	110	19	20	3	0.47	15	0.05	2	0.60	20	0.60	20	1.72	57
5	F	7	113	26	20	3	0.57	19	0.55	19	0.55	18	0.60	20	2.27	76
6	M	6½	113	18	21	3			0.61*	20	0.73	24	0.46	15	1.80	60
7	F	7	118	23	23	3	0.35	12	0.41	14	0.60	20	0.40	13	1.76	59
8	F	8	118	23	23	3	0.49	16	0.80	27	0.66	22	0.17	6	2.12	71
9	F	7	120	21	24	3	0.41	14	0.53	17	0.52	17	0.38	13	1.84	61
10	M	10	125	29	26	3	0.53	18	0.64	21	1.01	34	0.30	10	2.48	83
11	F	9	127	24	28	3	0.34	11	0.52	17	0.54	18	0.47	16	1.87	62
12	F	12	135	30	32	3			1.40*	47	0	0	0	0	1.40	47
13	F	9	135	34	32	4			1.60*	40	1.24	31			2.84†	71
14	F	11½	140	38	36	3	0.54	18	0.92	31	0.64	21			2.10†	70
15	F	13	140	36	37	4	0.69	17	0.96	24	0.94	24	0.31	8	2.90	73

*Excreted in this and preceding hour.
†Total for three hours only.

TABLE V

HIPPURIC ACID TEST IN CHILDREN WITH CLINICAL OR SUSPECTED HEPATIC DISEASE

NO.	SEX	AGE (YR.)	HEIGHT (CM.)	ACTUAL WEIGHT (KG.)	IDEAL WEIGHT (KG.)	DIAGNOSIS, REMARKS	DOSE OF SODIUM BENZOATE (GM.)	HIPPURIC ACID EXCRETED									
								1ST HOUR		2ND HOUR		3RD HOUR		4TH HOUR		TOTAL	
								GM.	%	GM.	%	GM.	%	GM.	%	GM.	%
1	M	5	?	?	?	Gargoylism	3	0.14	5	0.24	8	0.45	15	0.65	21	1.48	49
2	M	6	110	19	20	Diabetes mellitus, catarrhal jaundice	2	0.20	10	1.03	51	0.29	15			1.52*	76
						Recovered	2	0.77	38	0.72	36	0.31	16	0	0	1.80	90
3	M	11	133	24	30	Catarrhal jaundice, 4/6/38	2.5	0	0	0.29	11	0.34	14	0	0	0.63	25
						Test repeated, 4/7/38; 3 Gm. glycine added	2.5	0.75	30	1.08	43	0.35	14	0.04	2	2.22	89
						Recovered, 4/14/38	2.5	0.72	29	1.03	41	0.40	16	0	0	2.15	86
4	M	8	123	24	26	Catarrhal jaundice	3	0	0	1.05	35	0.26	9	0.49	16	1.80	60
						Recovered	3	0.43	14	0.72	24	0.79	26	0.30	10	2.24	74
5	M	13	158	44	50	Catarrhal jaundice	4	0.57	14	1.10	28	0.98	24	0.42	11	3.07	77
6	F	12	158	37	50	Banti's disease, hepatosplenomegaly	4	0.54	13	0.86	22	0.53	13	0.44	11	2.37	59
7	M	7	130	25	28	Banti's disease, splenomegaly	4	0.40	10	0.59	15	0.57	14	0.35	9	1.91	48
8	F	6½	?	20	?	Banti's disease, cirrhosis of liver	3	0.51	17	0.81	27	0.28	9	0.40	13	2.00	66
9	M	7	118	23	23	Diabetes mellitus, hepatosplenomegaly	3	0.51	17	0.65	22	0.97	32	0.12	4	2.25	75

*Total excretion for three hours.

control results. Thirteen of these subjects who had ideal weights between 15 and 40 kg. received 3 Gm. of sodium benzoate. Based on our findings in the first two control groups, nine of these patients had low excretions. We can only conjecture on the possible reasons for this. The repeated upper respiratory infections to which these children were subject may have been responsible. Indeed, the two children in Group 2 who were examined while convalescing from such infections eliminated low quantities of hippuric acid. Poor dietary regimes of some of these children, who were all clinic clients, may have also played a role.

RESULTS IN PATIENTS WITH CLINICAL OR SUSPECTED HEPATIC DISEASE

This group includes nine patients who had clinical signs or symptoms of liver involvement. Some of the tests on these children were done before the decision to use 3- and 4-Gm. doses, so that in some instances the sodium benzoate was not used in the standard quantities. Patient 1, a 5-year-old boy with the condition of gargoylism, eliminated 49 per cent

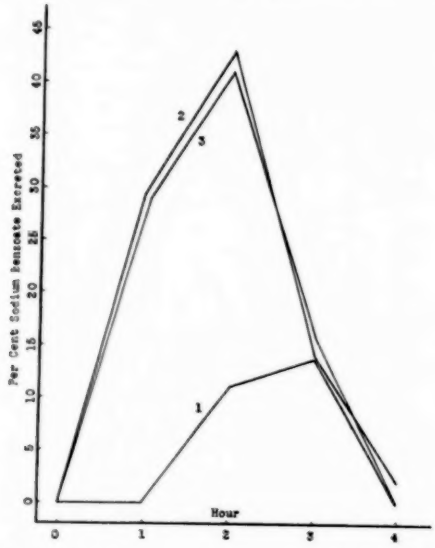

Fig. 2.—Patient 3, Table V. *1*, Impaired function in catarrhal jaundice; *2*, normal response during illness when glycine was administered with benzoate; *3*, normal function following recovery.

of a 3-Gm. dose in four hours, thus showing impaired function. Patient 2, a diabetic patient, was examined with only 2.5 Gm. during the course of an attack of catarrhal jaundice. The test was repeated with the same dose after the patient's recovery. During the course of the catarrhal icterus the test showed a lag during the first hour, and in three hours 61 per cent was eliminated. After recovery, this first-hour lag disappeared

and the patient was able to excrete 72 per cent in three hours. Two other children with catarrhal jaundice (Patients 3 and 4) gave abnormal results during the course of the illness and normal findings after recovery, while a fourth case (Patient 5) gave practically normal findings. In Patient 3, the test was repeated during the illness with a mixture of glycine and sodium benzoate. The addition of the glycine enabled the liver to synthesize hippuric acid at a normal rate, as shown by the practically identical findings after the patient's recovery (Fig. 2). Thus, in this instance it was the glycine-mobilizing mechanism that was disturbed, while the conjugation process was unimpaired. Judged from the hippuric acid test, one can conclude that catarrhal jaundice leaves no permanent damaging effects on the liver.

Two children (Patients 6 and 7) suffering from Banti's disease showed definite impairment of the liver function, while a third (8) gave borderline results. Patient 9, a diabetic child with hepatosplenomegaly of undetermined cause, showed normal results.

CONCLUSIONS

Three grams of sodium benzoate are sufficient for gauging the maximum rate at which the liver can synthesize hippuric acid in children whose ideal weights for height and age range from 20 to 40 kg. The adult dose of 4 Gm. is necessary for children whose ideal weights are 40 kg. or over.

Twenty-five control subjects, with ideal weights of from 20 to 40 kg., receiving 3 Gm. of sodium benzoate, eliminated from 67 to 88 per cent of the benzoate in four hours, with an average of 79 per cent. Twenty-two of these subjects excreted from 32 to 58 per cent during the first two hours, with an average of 46 per cent.

Ten control subjects, whose ideal weights were 40 kg. or over and who ingested 4 Gm. of sodium benzoate, excreted from 69 to 92 per cent in four hours, with an average of 82 per cent. For the first two hours, these children eliminated from 41 to 74 per cent, with an average of 52 per cent.

Tests were performed in fifteen children admitted to the hospital for tonsillectomy. Nine of these subjects gave low values.

Disturbed function was demonstrated in two cases of chronic arthritis, in two children recovering from acute upper respiratory infections, in one patient with aniline dye poisoning, and in one child who had had a nephrectomy for Wilms' tumor of the kidney.

Three of four patients with catarrhal jaundice had impaired hippuric acid functions. Examination of one of these patients with a mixture of glycine and sodium benzoate showed that in this condition, the glycine-mobilizing mechanism is defective, while the conjugating function is unimpaired. In children recovered from catarrhal jaundice the hip-

puric acid test gives normal results. Disturbed liver function was found in two of three subjects suffering from Banti's disease, and in one case of gargoylism.

We wish to express our appreciation to Miss Edith Bateman, Superintendent of the St. Louis Shriners' Hospital for Crippled Children, and to Dr. Alexis F. Hartmann of the St. Louis Children's Hospital.

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NEURAL MATURATION OF THE INFANT AS EXEMPLIFIED IN THE RIGHTING REFLEX, OR ROLLING FROM A DORSAL TO A PRONE POSITION

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THE ability of the young animal to right itself, that is, to turn from a dorsal to a prone position, has been a subject of considerable interest to neurophysiologists since the publication of studies by Magnus[1] and Rademaker.[2] Actually, the righting reflexes are those which enable the animal to return the body or any part of the body to its normal position. The normal posture for four-legged animals means that the ventral surface of the trunk is on the ground side. Practically all vertebrates are equipped with neuromuscular mechanisms which allow them to make this adjustment if they are placed in a dorsal, lateral, or other unusual position. Magnus pointed out that there are several groups of reflexes which make these movements possible: (1) The "labyrinthine righting reflexes" provide for an orientation of the head in relation to space. In this instance, while the neuromuscular expression takes place in the neck muscles, the stimulus arises in the labyrinths. (2) In the "body righting reflexes acting on the head," the expression also occurs in the adjustment of neck muscles, but the stimuli arise from sense organs on the body surface. Under appropriate stimulation, the head tends to assume a normal position even though the body does not follow the movement. (3) The "neck righting reflexes" orientate the body in relation to the head and may involve expression in the entire vertebral column. Movements of the head evoke adjustments in the inferior portions of the axis, and it is the position of the head which acts as the exciting agent. Adjustments of the vertebral column tend to follow positions of the head. (4) The "body righting reflexes" serve to adjust the body in relation to the ground. These reflexes allow the body to make an adjustment with respect to an external surface, independent of the position of the head. In other words, movements of the body attain some degree of "individuation" and are not completely dominated by head position. (5) In higher mammals the "optical righting reflexes" serve to facilitate orientation of the body with respect to its environment and the adjustment of parts of the body in relation to the whole. Some species, e.g., the rabbit and guinea pig, do not make use of the eyes for righting purposes. All of these reflexes are concerned with the adjustment of parts of the body with respect to the vertebral axis, as well as adjustment of the entire body with respect to space.

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In order to determine the several components of a complete righting response in animals, Magnus found it necessary to ascertain a "zero condition;" that is, by destruction of all sensory sources, the animal was reduced to a state where no righting tendency could be elicited. This procedure was experimentally necessary since even the newborn of most mammals are able to right themselves. In studying the early righting mechanisms of the human infant, the experimenter is fortunately provided with a "zero condition." Unlike the newborn of other species, the neonate is unable to turn from a supine to a prone position. Moreover, since the newborn infant is unable to hold his head up, functioning of the labyrinthine reflexes is questionable.

Obviously, turning from a supine to a prone position does not consummate the righting response for the human being whose normal position places the vertex upward. But many behavior activities of the infant appear to be a phyletic heritage, and rolling over may be a residual of the righting response common to quadrupeds. In the infant it is a precursor of the human righting response, and in the early stages of that activity it is, in most instances, a component of the assumption of an erect posture. For that reason, no study of development in the assumption of an erect posture is complete without taking into account the developmental sequences involved in rolling from a supine to a prone position.

The present study embraces an analysis of significant changes in these muscular movements. Seventy-five infants were observed at repeated intervals during the first two years, and records were made of any effort, either stimulated or spontaneous, to roll from a dorsal to a prone position. A total of 1,840 observations were recorded, of which 749 were on motion picture film. In addition to the group data, daily observations (five days a week) were made upon four individual infants for the purpose of obtaining longitudinal data on the development of this activity. Observations on the rolling behavior of infants in a supine position were supplemented by observations on neuromuscular adjustments in several suspended positions—suspended prone, dorsal, lateral, vertical, and inverted. While these reactions are not embodied in this report, they have been of aid in appraising the components of the righting response.

Although it has not been possible to assess the reactions in terms of detailed sensory components as Magnus has done for the righting reflexes of animals, the neuromuscular changes exhibited by the infants can be evaluated so as to determine periods of major reorganization of the neural levels involved. During the early efforts of the infant to roll over, many of the movements display some of the principles implied in Magnus' analysis of the righting reflexes. It appears that the early rolling pattern of the infant is a result, to a large extent, of the integration of these various labyrinthine and proprioceptive righting reflexes.

Rademaker[2] has demonstrated that in lower animals the integration of the righting reflex takes place in the midbrain at the level of the red nucleus.

The criteria employed in rating the observations on the growing infant were based upon the pattern of overt performance and not upon an appraisal of the reflexes involved. The following descriptions of four significant phases will clarify the criteria.

DEVELOPMENTAL PHASES IN ROLLING FROM A DORSAL TO A PRONE POSITION

A. The Newborn Phase.—Although the newborn infant is unable to turn from a supine to a prone position, varying degrees of tension exhibited by different groups of muscles are often such that the baby may roll from a dorsal to a lateral position. Differences in tone of several muscular groups set up an action and gravitational force supplements it to such an extent that the baby appears to roll from back to side. This reaction can frequently be observed as a component of the Moro reflex.[3] It seems clear that it is not a part of the body rolling or righting mechanisms. It is a total body rather than a segmental response. Such diffuse movements become diminished during the first few weeks of life. Then for a period the infant tends to lie in the supine position and makes no observable effort to rotate the body. He may turn the head somewhat toward the left or the right, but the movement is an isolated one which does not affect other parts of the body. In this study both of these types of behavior have been given a plus rating in phase A since they do not presage the righting movement. This phase is illustrated by line drawings *A* in Fig. 1.

B. The Spinal Extensor Phase.—Within the course of a few weeks, it is observed that the baby not only turns the face laterally, but extends the neck dorsally. This movement tends to raise the shoulder on the side toward which the occiput is turned. Gradually the extension expands caudad until it embraces the entire vertebral column, resulting in a dorsal curvature of the spine as the foot on the occiput side pushes against the surface and lifts the pelvis. As this phase develops, the extremities, both upper and lower, on the occiput side are lifted and carried over toward the chin side. The shoulder and hip are raised until the infant is lying practically in a lateral position. Ordinarily the rolling movement is initiated in the shoulder girdle. At such times the infant may flex his neck ventrally in an effort to complete the roll. Unless the flexor movement is accurately timed, it is likely to toss him back into a dorsal position. Later the initial movement may take place in the pelvic region as the shoulder lags behind. The child tends to throw the leg over toward the chin side without much initial pushing and without marked spinal extension. In such instances, the pelvic girdle may closely approximate the prone position, while the shoulder girdle is still approaching a lateral position. The criteria for phase B embrace all spinal

extensor movements preparatory to a complete roll from the supine to the prone position. Illustrations of this phase are designated in *B* of Fig. 1. Finally, the baby is able to effect a complete roll into the prone position. When it occurs only occasionally and with considerable effort, a positive rating has been accredited to the following phase as well.

Fig. 1.—Line drawings illustrating four phases involved in rolling from a supine to a prone position.

C. The Automatic Rolling Phase.—When the child is able to complete the roll but apparently has no purpose in utilizing the movement to carry on some other function, such as assuming a sitting position, he has been credited a positive rating in phase C. During this phase the movement has an automatic quality which characterizes it more as an involuntary than as a distinctly deliberate act. Some endogenous impulse seems to activate the behavior. In most infants spinal extension is still pronounced as an initial move, but as development proceeds, the various components become so well integrated that it is difficult to detect just where the movement is initiated. Also there are a few infants who do not show marked spinal extension when they first achieve the act, although it had been exhibited previous to the actual rotation. Such infants usually turn over by flexing the legs on the abdomen and flexing the spine as they turn. Even in these children the act of rolling has the characteristic automatic quality which distinguishes it from a deliberate

performance. During this phase the infant does not adjust himself in accordance with the space on which he rolls. Unless protected, he may roll off the bed without evidence of caution or inhibition.

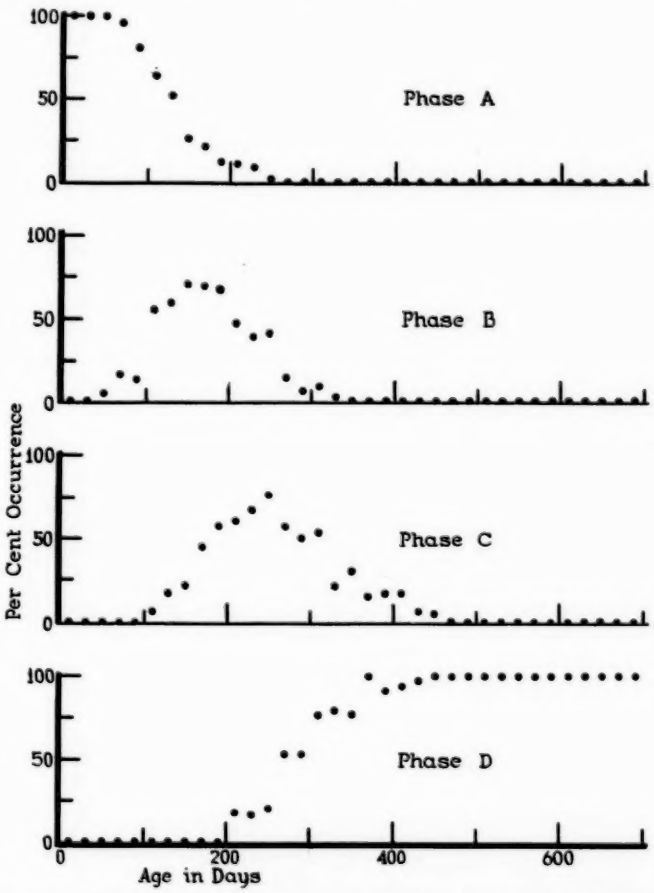

Fig. 2.—Curves showing the percentage occurrence of each phase at each twenty-day interval.

D. The Deliberate Phase.—The characterizing feature of this phase is that the child begins to use the act of rolling over for the purpose of completing some deliberate performance. As soon as he has turned, he begins to flex the legs and raise the abdomen in order to creep or push into a sitting position. Also at this time the child shows some tendency to adjust himself in accordance with the allotted turning space. Such adjustments indicate functioning of the "optical righting reflexes." That the act of rolling at this stage becomes an integral part of the ultimate human righting response (expressed in the achievement of an

TABLE I

TOTAL NUMBER OF OBSERVATIONS IN EACH TWENTY-DAY INTERVAL

AGE AT MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	AGE AT MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS
10	125	370	40
30	56	390	35
50	51	410	36
70	56	430	36
90	63	450	37
110	83	470	29
130	58	490	30
150	47	510	20
170	47	530	25
190	51	550	30
210	45	570	33
230	54	590	35
250	49	610	24
270	49	630	30
290	34	650	34
310	47	670	29
330	42	690	20
350	43	710	17

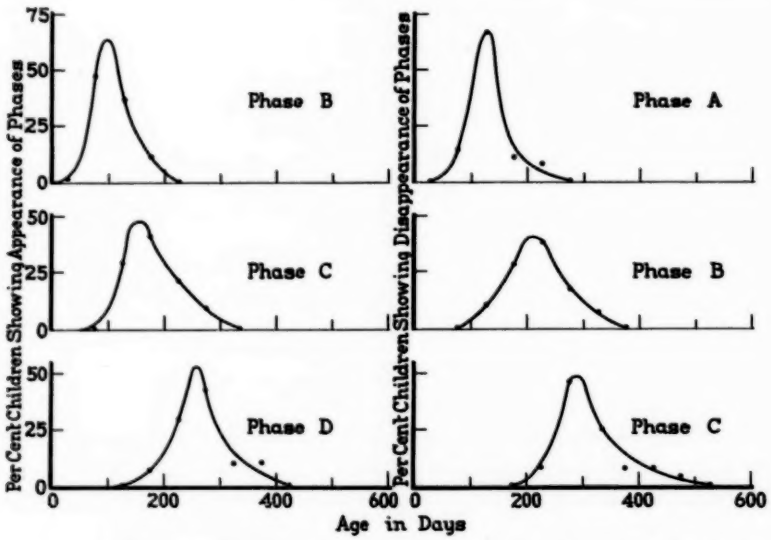

Fig. 3.—Distribution curves showing the percentage of children manifesting a change in phase at each age interval.

erect posture) is demonstrated when the infant persists in carrying the movement to a hand-knee or sitting position before actually reaching for the stimulating lure. After both functions are thoroughly developed, the child may then exercise his choice and engage in no more neuromotor activity than is necessary to obtain the object of his attention. However, in this analysis both types of behavior have been rated as

representative of phase D since they both express purposeful and deliberate qualities in the rolling movement.

ANALYSIS OF THE DATA

After the observations were rated according to the above criteria, it was possible to determine the percentage of times each phase was represented in any given age interval. Table I indicates the number of observations at each twenty-day interval. Only those observations made dur-

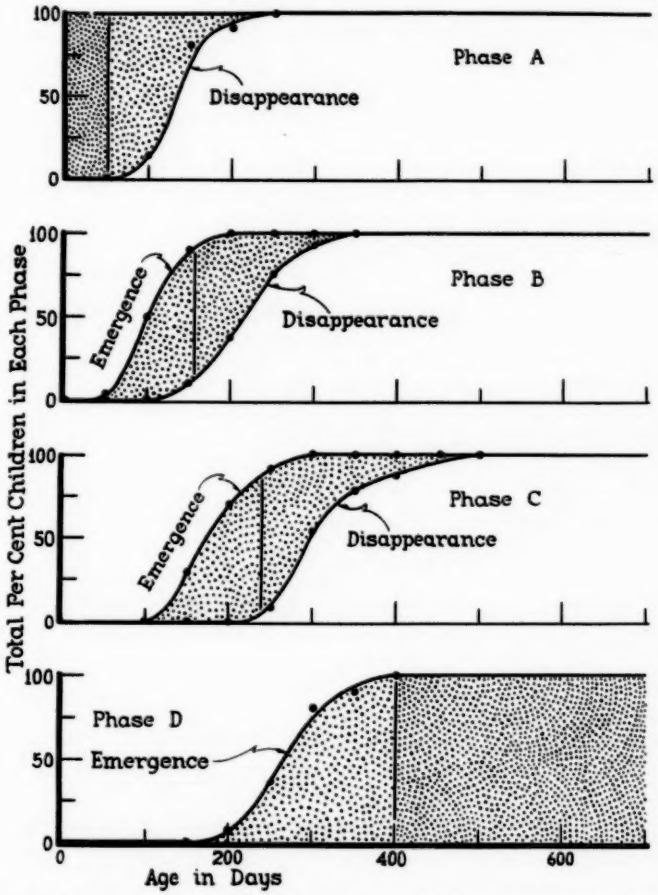

Fig. 4.—Ogives representing the total percentage of children who have manifested (1) the emergence and (2) the disappearance of each phase at any age interval. The dotted area indicates the percentage of infants exhibiting a phase at any given time.

ing the first 710 days are represented in this report since no significant changes were evidenced in the later records. The incidence of each phase as represented by the group is shown in the curves of Fig. 2. From

these curves it can be seen that the youngest child to complete the act of rolling from a dorsal to a prone position was approximately 4 months old, and the youngest to manifest a deliberate quality in the act was

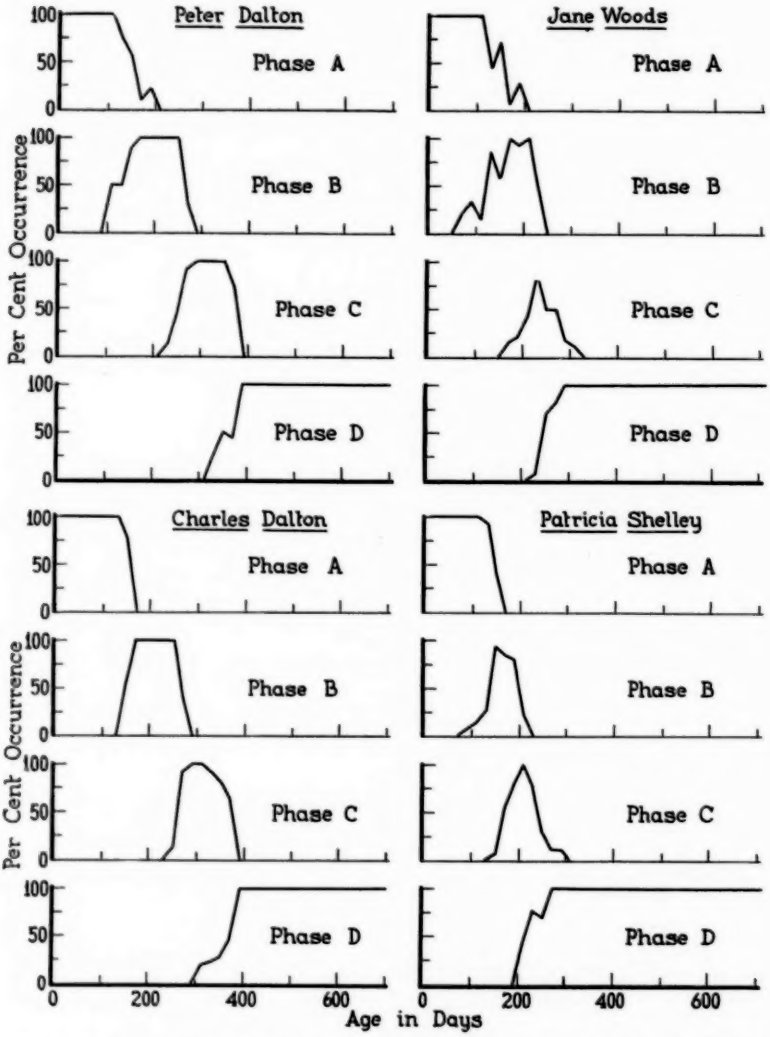

Fig. 5.—Curves showing the incidence of each phase as manifested by four individual infants, two of whom were identical twin boys.

approximately 7 months old. The distribution curves in Fig. 3 show the percentage of children manifesting a developmental change at any age interval. The ogives representing the total percentage of children who

had shown the emergence and evanescence of each phase at any age interval are shown in Fig. 4. The shaded areas indicate the total percentage of children manifesting a phase at any given time. At approximately 5½ months of age, the greatest number of children exhibited the extensor phase, preparatory to the act of rolling over. By the age of 8 months most of the infants were rolling completely over, but primarily in an automatic manner; by the end of the first year all of the children had acquired a deliberate quality in the performance.

That the trend of development, as manifested by the intensive study of individuals, is essentially the same as that shown by the group is demonstrated by the curves in Fig. 5. These curves represent the percentage of occurrence of each phase within any twenty-day interval. Despite the fact that these curves represent unsmoothed data, and despite individual variation in chronologic age with respect to the onset and achievement of any particular phase, the trend of development as represented by the longitudinal data on individual infants is essentially the same as that manifested by the group.

DISCUSSION

In view of the series of reflexes involved in the righting response as analyzed by Magnus, it is reasonable to assume that the onset of phase B, which corresponds to the time when the infant gains some control over the position of his head in relation to gravity, denotes the early development of sensory stimulation arising in the labyrinths. This development of control over position of the head with respect to space was well demonstrated in the suspended positions. Likewise, this phase reflects the functioning of the neck righting reflexes. At this time the body tends to move in accordance with the position taken by the head. Toward the end of this phase, the "body righting" reflexes are brought into play, as evidenced by the child's initial turn of the pelvis, as he throws the leg over, before the movement is begun in the head or neck region. During the early part of phase B the head position tends to dominate movements of the trunk, but toward the latter part of the phase movements of the pelvis and lower extremities achieve some "individuation" with regard to head movements. If, during the early extensor phase, the head is passively turned, it will be observed that the shoulder tends to rise also; whereas in the latter part of the phase, the shoulder and pelvis appear to be liberated from influence of such passive movements of the head. According to Fulton,[4] the "labyrinthine and body righting reflexes acting on the head" (early part of phase B) are integrated in the midbrain at the level of the red nucleus; the "neck righting reflexes" (phase B and the early part of phase C) are integrated in the medulla; and the "optical reflexes" (phase D), in the cortex. On the basis of overt behavior, the automatic qualities of the movements reflected in phase C suggest that the early rolling movements are mitigated at a nuclear level. Although the movements during this

phase become quite integrated, they still display the automatic quality, whereas the purposive or deliberate qualities of phase D denote active participation of the cerebral cortex in the initiation and conduct of this performance. Functioning of the "optical righting mechanisms" provides additional evidence that the optic cortex is participating in the activity.

It appears then that the righting response in an infant is composed of a complex series of reflexes developing in a cephalocaudal direction. After the series of reflexes attains a degree of integration at a nuclear level, the cerebral cortex gains dominance and the function becomes incorporated into the human mode of the righting response, viz., the assumption of an erect posture. Although observations on developmental changes in erect locomotion and the assumption of an erect posture[5] were made under different conditions, the first signs of cortical participation in these activities occurred about the time deliberate rolling over was achieved, as revealed in these data. Evidence of cortical functioning was indicated in these activities by most of the children between the eighth and ninth months. As the human righting response matures, rolling over becomes eliminated as an initial move in the performance.

SUMMARY

Neuromuscular changes as exhibited by seventy-five infants in the achievement of an ability to turn from a supine to a prone position have been described. A total of 1,840 observations have been rated in accordance with criteria which differentiate four significant phases. The group data are supplemented by longitudinal data on four individual infants. Curves showing the age period when each phase is the characteristic mode of behavior are presented.

Changes in the pattern of behavior as they reflect the "righting reflexes" described by Magnus have been discussed. It has been suggested that the rolling response is perhaps in the infant a phyletic activity which becomes integrated at a nuclear level before cortical dominance occurs. Subsequently, it is utilized as a component of the human righting response, i.e., the assumption of an erect posture. As the latter behavior matures, the rolling over phase tends to become eliminated or at least diminished.

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II. THE EFFECT OF COOKING ON THE DIGESTIBILITY OF CEREALS

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IN A previous paper the effect of cooking on the enzymatic digestibility of the starches of various cereals was reported.[1] The procedure was to take a measured amount of the cereal to be tested, add a constant amount of water, and cook for varying periods of time, up to four hours. An amount of pancreatic enzyme sufficient to produce the maximum amount of maltose from the starch was added. The digestion was allowed to proceed at 37° C. for one-half hour. The reducing substances were then determined by Willstätter's iodine titration method.[2]

In a reinvestigation of Willstätter's method, it was found that certain unsuspected errors were present. In this method an amount of iodine more than required to react with the reducing substances is added, and the excess is titrated with sodium thiosulfate. The maltose is calculated on the basis of the iodine removed by the reducing substances. It was found that the amount of iodine removed in any given digest was influenced by the excess of iodine present. This factor was not recognized in calculating the results in the previous paper.

A further investigation of the entire problem was made. The Harding-Downs modification of the Shaffer-Somogyi copper reduction method was used, to avoid the errors encountered with the Willstätter method. To use the Harding-Downs method it was necessary to treat the digests with West's mercuric sulfate reagent to remove interfering substances. With this method the titration values are directly proportional to the amount of maltose present. It was considered that the rate of digestion of the starch in the cereal after cooking would be a more sensitive index of the digestibility of the cereal than was the previous method of measuring the maximum conversion. For this reason, a smaller concentration of enzyme was used and digestion was allowed to proceed for varying periods of time in successive samples. The percentage of starch converted to maltose in the samples was then plotted against the time of digestion to give a curve expressing the rate of conversion of starch to maltose under these conditions.

PROCEDURE

The following procedure was used for the determination of the total starch in the cereals: A 100-mg. sample of cereal was hydrolyzed with 25 ml. N HCl by boiling for two hours under a reflux condenser. The solution was then neutralized with approximately 1 N NaOH until

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slightly acid to litmus, transferred quantitatively to a 500-ml. volumetric flask, and diluted to volume. An aliquot of about 50 ml. of this diluted solution was acidified with one drop of 1:1 H_2SO_4 and shaken for about four minutes with 0.5 Gm. of Lloyd's reagent. The mixture was then filtered and the acidity adjusted to about pH 5.0 with 40 per cent NaOH and glacial acetic acid. The total reducing value of this solution was then determined by the Harding-Downs modification of the Shaffer-Somogyi method.[3]

A blank determination was run at the same time. In this the sample of cereal was allowed to stand in water for two hours at room temperature and then diluted to 500 ml. A 50-ml. aliquot was "cleared" with Lloyd's reagent and the reducing value was determined exactly as outlined above. The blank was zero in all cases except with the pablum. When the blank was zero, the total reducing value of the hydrolyzate was calculated as the number of grams of glucose per 100 Gm. of cereal. This value was then converted to the percentage of starch in the cereal by multiplying by 0.90 (since 1 Gm. of glucose is produced by 0.90 Gm. of starch).

An investigation of the reducing material giving rise to the blank in the pablum was undertaken. One hundred milligrams of cereal plus 50 ml. of water was allowed to stand, cleared by Lloyd's reagent as above, and the filtrate adjusted to pH 6.0 to 6.5. The total reducing value of this solution was determined. Ten milliliter aliquots of the filtrate were fermented with *Marxianus sacchromyces* and by *M. tropicalis*, following the procedure for mycologic analysis given by Harding and Nicholson.[4] *M. sacchromyces* removes only glucose, whereas *M. tropicalis* removes maltose as well as glucose. As a result of this, it was found that the reducing blank of pablum was due entirely to maltose, since fermentation by *M. sacchromyces* had no effect on this reducing value, whereas fermentation by *M. tropicalis* removed it completely.

This information was used in the calculation of the amount of starch in the precooked cereal. The total reducing value after hydrolysis was calculated as glucose. From this total glucose value was subtracted the amount of glucose that would have resulted from the hydrolysis of the free maltose found in the cereal. The residual glucose value was then multiplied by 0.90 to convert it to the percentage of starch.

The actual estimation of the enzymatic digestibility of the starch was made by the following procedure: An amount of cereal calculated to contain 51.7 mg. of starch was accurately weighed out into each of five test tubes and 2.5 ml. of water was added to each. The tubes were tightly stoppered with nonabsorbent cotton and placed in a wire basket, with the bottoms as close together as possible. The basket was then placed over one opening in a steam bath, and the basket and tubes were wrapped in cloths so that the tubes were entirely surrounded by the

steam. They were cooked in this way for one hour and then cooled, and the water loss was replaced to make up the 2.5 ml. volume. The mixture was stirred with a stirring rod so as not to splash the cereal on the sides of the tube.

One milliliter of phosphate buffer (0.2 M, pH 6.8) and 0.2 ml. of 0.2N NaCl were added to each tube. The tubes were then placed in a water bath at 37° C. for about five minutes to bring them to the temperature of the bath. One-tenth milliliter of 100 mg. per cent pangestin (1:75 Difco) in 1 per cent $NaHCO_3$ was accurately added to four of the tubes. The contents were then mixed and incubated for exactly ten, twenty, forty, and eighty minutes from the time of addition of the enzyme. The action was stopped at the end of the incubation period by adding 0.25 ml. of West's reagent (30 per cent $HgSO_4$ in 10 per cent H_2SO_4). The mixture was neutralized with finely ground $BaCO_3$, transferred quantitatively to a 100-ml. volumetric flask, and diluted to the mark. A blank was prepared in the same manner except that the order of addition of the enzyme and the West's reagent was reversed and it was not incubated.

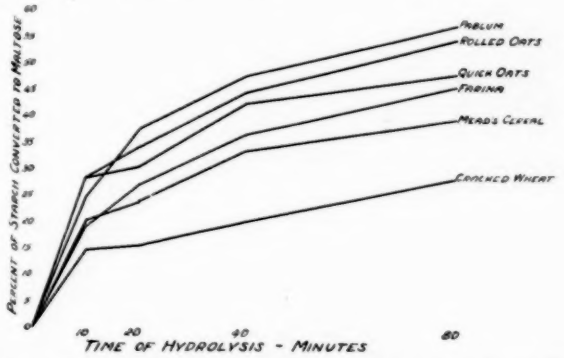

Chart 1.—Starch digestion of pablum and cereals cooked one hour.

The solutions were then filtered, acidified with one drop of 1:1 H_2SO_4 and about 100 mg. of lead acetate was added. H_2S was passed in to complete precipitation of the lead and mercury sulfides and the excess H_2S removed with a stream of nitrogen (or air). The solutions were filtered and the acidity adjusted with 18N NaOH and 1:1 H_2SO_4 to about pH 6.0. The reducing value was determined on 2-ml. aliquots, using the Harding-Downs method, and this reducing value was calculated as maltose.

The procedure with pablum was the same except that the cooking process was dispensed with, since this cereal is precooked.

The results obtained on a number of different cereals are shown in Chart 1. It is seen there is a significant difference in the rate of

starch digestion under constant conditions in the different cereals, cracked wheat having the lowest and pablum the highest rate of starch digestion.

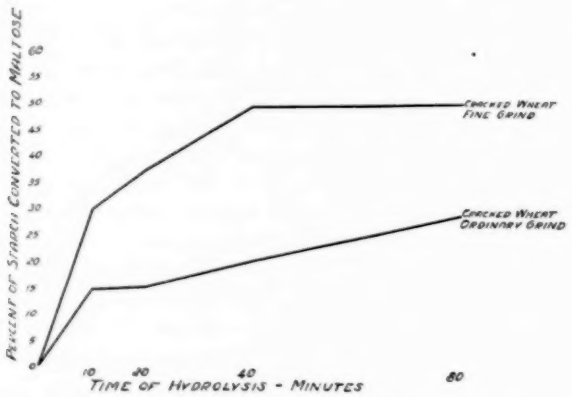

Chart 2.—Effect of the physical condition of cereal on starch digestion.

In Chart 2 is shown the rate of digestion of starch in cracked wheat as ordinarily purchased and also in the same cracked wheat finely ground. From this it is evident that the ease of digestibility of the starch is dependent, to some degree, on the physical state of the cereal. In this regard, it is of interest to note the difference in the rate of starch digestion between Mead's cereal and pablum. Both products have the same composition, but in the process of manufacture pablum is so treated that the final product is extremely porous. This no doubt accounts in no small measure for its ease of digestibility.

CONCLUSIONS

There is a significant difference in the digestibility of starch under constant conditions in different cereals. Changing the physical state of a cereal alters the ease of digestibility of its starch.

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BANANA DIET IN THE TREATMENT OF TYPHOID FEVER IN CHILDREN

Preliminary Report

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THE treatment of intestinal diseases, both chronic and acute, has been changing rapidly in the past few years. Outstanding in their popularity and justified by the results obtained from their uses have been the fruit diets and the fruit-milk diets. If we review the literature, we discover that the fruit diet for intestinal correction is not new in the past ten years or so, but rather that during this time it has been revised, improved and made desirable for use in a much broader scope of diseases.

A survey of the literature may justify somewhat the use of these diets in the treatment of typhoid fever by reason of giving information to show that these foods supply adequate caloric and mineral intake and fair vitamin requirements, as well as producing sufficient bulk in fecal material.

Alvarez and Hinshaw,[1] through a questionnaire, found that less than 15 per cent of the patients observed gave histories of any unfavorable reactions from eating bananas. Bailey[2] discusses the sterility of bananas. Fruit with intact skin has been immersed in fluid cultures of known bacteria for periods of forty-eight hours. The pulp of the banana thereafter cultured was still sterile. Bananas taken from push-carts, and probably not too clean ones, have been shown to have sterile pulp. Any food chosen for treatment should be clean. Sansum[3] lists the advantages of banana as a food because of its ability to combat acidosis by making available first a high, easily assimilated sugar, and second, a desirable buffer effect. Both of these qualities are desirable during a period of intestinal maladjustment. The yellow-green bananas have approximately 20 to 25 per cent starch. Brown-yellow bananas, however, contain 16 to 19 per cent soluble sugar, so it is necessary to choose the fruit with care or to bake the banana if the most desirable effects are to be obtained.

The nutrition value of the banana is about 400 calories per pound, according to Atwater and Bryant.[4] This is the highest caloric value per pound of any of the common fruits. When banana is combined with milk, the diet is close to complete. Many analyses have shown this fruit to be sufficient in vitamins A, B_1, B_2, C, and E. It has a low

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D factor, according to the report in 1932 of the Great Britain Medical Research Council. Evans[5] has shown by experiments on rats the clinical presence of sterility vitamin E.

Miller and Munsell[6] state that powdered banana retains its vitamin B components well, but that it shows no appreciable amount of vitamin C. Eddy[7] states that the vitamin C may be partly preserved by baking the banana in the skin. He further notes that banana appears to have the ability to stimulate the growth of gram-positive aciduric types of bacteria in the intestinal tract and to combat the development of the colon forms. Its value as a regulator of gastrointestinal function may in part be due to these properties. Its mildly laxative action is shown by its effect on the volume of the stools. It contributes to the diet significant amounts of the following minerals: calcium, magnesium, phosphorus, sulfur, iron, and copper, as evidenced by its effects on mineral metabolism. This is important, especially in a debilitating disease. It has hemoglobin and red blood cell regenerating potency, and it appears to have power to increase the utilization of lime when fed with sources of the bone and tooth building elements. This factor would be of especial interest to the pediatrician or the general practitioner who treats children ill with typhoid fever.

The literature holds an abundance of material regarding the use of banana in the treatment of celiac disease, diabetes, acute and chronic colitis, both ulcerative and nonulcerative types, acute and chronic gastric ulcers, sprue, scurvy, acute infections, diarrheal diseases, and nephritis. These reports agree that without question the diet is of important value. The reasons given for its satisfactory action are many: improved buffer action, improved sugar absorption, quick combat of acidosis, more adequate absorption and return to normal energy requirements, satisfactory pH in the stomach, more alkaline stools than result in milk diets, slowed emptying time of stomach, and due to pectin, swelling, which quality facilitates peristalsis, a proper emptying of ingesta to prevent stagnation in the bowel.

In the past few months I have had the opportunity to observe three children who were fed abundant amounts of banana while ill with typhoid fever. Two of these patients were under my care and the third was seen in consultation. Two of these cases were treated at home, and the data and laboratory reports are not as complete as I would like them to be. All three of these patients, however, were so severely ill during the first period of their illness that their improved general state following the institution of the fruit and fruit-milk diet impressed me especially, primarily because I did not expect such a change in so short a period of time with typhoid patients.

CASE 1.—A male child, aged 21 months, was brought to me for care. The history given was that the child had been well for the past month except for an abscess in the soft tissues of the right buttock which opened and drained about April 2,

1939. On the evening of April 20, 1939, the child developed a fever which mounted to 104° F. During the day he had had four or five stools, normal except that they were slightly loose. The temperature continued to be high, except when aspirin was given. I saw the child on April 21, 1939, before noon. By then he had had many loose stools, with much mucus. The stools were slightly more foul smelling than normal, and a few of them contained gross blood. The physical examination was essentially normal, except for acute flushing of the face and acetone on the breath. Because of his apathy, which was far from normal for him, the child appeared seriously ill. Obviously he was having occasional acute abdominal pains. The report of the stool examination at that time was as follows: The specimen submitted consisted mostly of mucus and pus. Occult blood was 2 plus; no ova or parasites were found. Cultures on Endo's media revealed many white, translucent colonies. Antityphoid serum showed marked agglutination in dilutions 1:3,500, 1:7,000, 1:10,000. Antiparatyphoid types A and B sera showed no agglutination. Antidysenteric serum for Shiga showed no agglutination, and for Flexner showed slight agglutination from 1:200 and no agglutination from 1:300. Unfortunately, no other laboratory examinations were obtained at this time.

The treatment recommended was as follows: One very ripe banana mashed or one apple finely grated every two hours, with as much buttermilk as the child would take. Water was to be given in abundance between feedings. Since the child objected to apple and buttermilk, the diet consisted almost entirely of banana. From April 21 to April 25, the temperatures as reported by the mother gradually declined, and the temperature was normal for the entire day on April 24. At the time of examination on April 25, the rectal temperature reading was 99.8° F. The number of stools had continued to decrease gradually and was approximately six daily. They were still loose and contained mucus and blood. On April 25, 1939, skimmed cow's milk, boiled with casec and appella added, was offered in the diet in addition to banana. It was impossible for the mother to keep the child in bed. He ate well, appeared improved, and desired to play. The stools continued in slightly increased numbers, however, green to yellow, watery, and with some mucus and blood for approximately two weeks. The Widal test taken on the ninth day was negative. Unfortunately, it was not repeated. Repeat stool culture, however, on May 9, 1939, was as follows: The stool contained shreds of mucus, many pus cells, small white translucent colonies on Endo's media, and was a yellowish-brown in color. Antityphoid serum gave marked agglutination in 1:3,500 dilution, while Flexner type serum, which had previously suggested positive infection, gave a negative agglutination in a dilution of 1:100. This patient continued from the fifth day of treatment to show constant improvement. Bananas were kept in abundance in the diet. Gradually cereal, protein foods, and sieved, cooked vegetables and fruits were added. The stools had returned entirely to normal by the end of one month. The temperature had been normal since the fifth day, except for one or two times when there were temporary elevations, and the stool culture was negative for typhoid bacillus at the end of a four-week period. The patient's gain in weight on May 16, 1939, represented 25 oz. over a period of five weeks, which included the period of illness. It was interesting to note that the maid in the home had a positive stool culture for typhoid, and one member of the family who had previously had the disease showed questionable positive stool findings on at least one examination. The child is now in apparently excellent health.

CASE 2.—On May 16, 1939, a male child, aged 4 years, previously in good health, became acutely ill. The illness began with vomiting early in the morning; the vomiting did not repeat. In a few hours, however, diarrheal stools began. There were eight stools in the first four hours; they were watery, with much mucus, brown

to green in color, and foul smelling. The child seemed to be extremely ill. He disliked taking anything by mouth because of nausea. The musculature of the entire body was uncontrollably active, and one might have said that he had a good case of the "jitters." His temperature at the time of first examination was 103.4° F. Physical examination was essentially normal, except for the findings already presented and apparently a slight tenderness in the abdomen on palpation. Treatment recommended was very ripe, raw, mashed banana and finely grated raw apple mixed, to be given every two hours in as large quantities as the child could take. Water was to be given in abundance. About eight hours later, the child was admitted to the hospital because his condition gradually seemed to be growing worse. His temperature was 105.4° F., and he refused food. Aspirin had been given while he was still at home, and one and one-half hours later the temperature reading at the time of hospital admission was 102.4° F. The blood count was as follows: hemoglobin, 90 per cent; red blood cell count, 4,520,000; leucocytes, 5,000; small lymphocytes, 10 per cent; large monocytes, 12 per cent; polymorphonuclear cells, 78 per cent. The throat culture was negative for diphtheria. On May 18, 1939, the stool specimen was reported semiliquid, with mucus, dark green in color. The microscopic examination revealed many pus cells and red blood cells and mucus. Motile gram-negative bacilli were present. E and M plates revealed nonacid-forming organisms. There was a negative agglutination with Shiga and Flexner sera. The agglutination for typhoid bacillus was positive.

On admission to the hospital, Hartmann's solution with 5 per cent glucose was given subcutaneously, and oral Hartmann's solution was also administered. Grated raw apple and finely mashed ripe banana were alternated in feedings every two hours, beginning on the morning of May 17, 1939, the second day of his illness. The temperature varied from 99.6 to 101° F. until late in the afternoon of May 18, at which time the reading was normal. There was no elevation of temperature after he left the hospital on May 19. The mother checked the temperature by rectum every four hours.

On May 19, skimmed boiled milk, with appella added, was substituted for grated raw apple and was given along with the banana feeding. The stools continued to be typical typhoid pea-soup stools, gradually decreasing in number per day; by the end of the third week, the stools were normal in consistency and number. The primary difficulty encountered in the child's care was to supply satisfactory quantities of soft foods at frequent enough intervals. Keeping him in bed became almost an impossibility. At the end of the third week, five stitches were taken in his shoulder to repair a cut which he received while doing acrobatics. Two successive cultures of the stool at four weeks were negative for typhoid. His weight loss was approximately ½ pound.

CASE 3.—A male child, aged 8 years, became ill six days before entrance to the hospital on May 24, 1939. The temperature ranged from 101 to 102.5° F. He complained of generalized abdominal pain. There was a nonproductive cough, sometimes causing chest pain. Nausea and vomiting were symptoms present occasionally, and anorexia and malaise were outstanding symptoms. The digestive symptoms have persisted from the onset. The past history noted that the child had had tonsillectomy and adenoidectomy, measles, whooping cough, and anemia. The parents stated that the child had always been sick. The family history was essentially negative. The physical examination revealed the following points of interest. The child was slightly malnourished. In the lungs a slight roughness of the breath sounds could be heard over the right apex. The spleen was enlarged and palpable. The child's sensorium was clouded. He was irrational at times and appeared to be extremely ill, with marked abdominal discomfort. Each day, according to the history, there

were from two to four loose, yellow stools. X-ray of the chest showed no gross lung lesion. Further examination of the chest gave no increased positive finding. The blood count on May 25, 1939, was as follows: hemoglobin, 80 per cent (Sahli); erythrocytes, 3,950,000; leucocytes, 10,400; small lymphocytes, 29 per cent; large monocytes, 1 per cent; polymorphonuclear cells, 70 per cent. The urine examination on May 25, 1939, was normal, except that it was positive for acetone. The Widal agglutination test was positive in a dilution of 1:160 on May 24, 1939. The stool culture on May 20, 1939, was negative.

The blood culture on May 29, 1939, was positive for typhoid. The urine culture and stool cultures were both normal on June 10 and 12, 1939. The white blood count varied from 6,600 to 11,200, and the lymphocyte count varied from 29 to 64 per cent. The urine remained normal except for positive acetone and diacetic acid at varying intervals. The temperature curve was septic in type and varied from 100.4 to 106.4° F., even though abundant fluids were given parenterally and aspirin was used freely. On June 1, the temperature curve remained between 103.2 and 104° F. On June 2 the temperature elevated to 105.8 at 4 P.M. The child was put on a diet of banana and buttermilk. Cevitamic acid, 150 mg. daily, supplemented the diet. After a period of forty-eight hours, the temperature began a staircase decline until June 7, at which time it elevated sharply to 105° F. for one reading and dropped abruptly to 99.6° F. by rectum. The temperature remained between 98.6 and 100° F. for the remaining nine days of hospitalization except for one brief period of elevation on June 12, which the attending physician attributed to constipation and abdominal distention. No antipyretic drug was given, and the temperature was reduced to normal within twelve hours following a cleansing enema. No new food was added to the diet until June 13. The stools began improving about June 4, 1939. During the first week the child had some discomfort with gas and distention. This child was not weighed on discharge. However, the physician notes on the chart that the weight loss was obviously very slight.

SUMMARY

Banana, especially when supplemented by skimmed milk or buttermilk, makes a desirable food for the maintenance of nutrition in typhoid patients. It supplies caloric requirements, minerals, and vitamins, and is apparently readily digestible.

The temperature curve decreased strikingly in from two to five days, even though the stools did not show such prompt improvement.

The general well-being of the patient was markedly improved. The period of acute symptoms was shortened.

In these three cases the stools were negative for typhoid in from three to four weeks after onset of symptoms.

Because of the limited number of cases observed, and because treatment in two cases was started before the diagnosis of typhoid was made, many observations, corrections, and additions to this suggested treatment undoubtedly can be made. I am definitely of the opinion that it deserves continued investigation.

NOTE: Since the completion of this paper, Dr. Elton Charvoz has reported a fourth case to me, that of an 11-year-old girl whose recovery from typhoid was equally satisfactory on the suggested treatment.

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Critical Review

TUBERCULOSIS IN CHILDHOOD

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EVALUATION OF THE TUBERCULIN TEST

OF THE many contributions to tuberculosis literature for the year, the most controversial is that of Lumsden, Dearing, and Brown.[1] A survey of tuberculosis in Tennessee and Alabama leads these authors to the conclusion that skin testing as a means of establishing the epidemiologic index or rate of incidence of tuberculous infection is of questionable value or is definitely futile. The survey was conducted in Giles County, Tennessee, where the annual death rate from tuberculosis per 100,000 population was 116 among whites and 210 among negroes. At the same time a survey of Coffee County, Alabama, was conducted where the mortality rate was 12.5 among the white population and 5.4 among the negroes. In testing 3,900 school children with one-tenth the second strength of purified protein derivative (P.P.D. 0.0005 mg.), it was found that despite the marked difference in the tuberculosis mortality rates in the two counties, the number of reactors to the Mantoux test was almost the same. In Giles County, Tennessee, 13.8 per cent of the white children and 22.4 per cent of the colored children reacted, and in Coffee County, Alabama, 14.9 per cent of the white children and 19.5 per cent of the colored children reacted. It had been anticipated that from 40 to 60 per cent of the children in Giles County, Tennessee, would prove to be positive reactors. In view of the low percentage of reactors, it was concluded that there was something wrong with the supply of P.P.D., although it had been obtained from Company A, which is one of two companies manufacturing and distributing P.P.D. under authentically approved conditions.

To check the efficacy of the P.P.D. of Company A, a sample was sent to the National Institute of Health, where it was reported that the sample, used on sensitive guinea pigs, gave reactions comparable to those of the P.P.D. used there for testing. As an additional check, the authors conducted tests with full second strength P.P.D. of Company A and other tuberculin preparations, and duplicate tests with the original P.P.D. preparation and with one of the following preparations: lot 511 of old tuberculin (O.T.) of Company B; lot 771 of O.T. of Company B; a lot of O.T. from the Michigan State Health Department; and P.P.D. obtained from Company C. A total of 701 children in several schools who were negative to one-tenth the second strength of P.P.D. were retested. Of 333 retested with a full second dose of P.P.D., 11.7 per cent were positive; of 164 retested with lot 511 of O.T., 31.1 per cent were positive; and of 204 children retested with lot 771 of O.T., 80.9 per cent were positive. Duplicate tests on opposite forearms were done on 450 children with one-tenth the second strength of P.P.D. of Company A on one arm, and a

similar dose of another preparation used on the other arm. The results were: 11.8 per cent reacted to P.P.D. of Company A; 52.6 per cent reacted to lot 511 of O.T.; 78.6 per cent reacted to lot 771 of O.T.; 19.4 per cent reacted to O.T. from the Michigan State Health Department; and 31.4 per cent reacted to P.P.D. of Company C.

"These strikingly variable results indicate that different preparations of tuberculin now used extensively by our health agencies vary greatly in potency and specificity and signify that the percentage of positive reactors among school children, and inferentially among other general population groups, depends largely upon the particular preparation of tuberculin used in making the tests. Satisfactory epidemiological measurements cannot be made with such varying yardsticks."[1]

Another startling finding in the survey was that the x-ray evidence of calcified pulmonary areas was over forty times as high in Giles County as in Coffee County. However, in Giles County calcified areas were nearly as frequent among those reacting negatively as among those reacting positively to routine testing with P.P.D. of Company A. Thus, x-ray is a much more reliable epidemiologic index than skin testing.

Lumsden and his co-workers conclude: "Further work, both laboratory and field, by properly equipped agencies for the determination of reliable standards of potency, specificity, uniformity and stability of tuberculin preparations, and for the establishment of reliable standard methods of administration and interpretation of tuberculin tests among persons, is highly in order."

Crimm and Short,[2] in a study at Evansville, Ind., report 191 patients with roentgenologic evidence of pulmonary calcification who were anergic to diagnostic doses of tuberculin. However, over a four-year period, four patients manifested either a reinfection or a return of allergy as indicated by the tuberculin tests.

In an endeavor to determine the cause of the discrepancy between P.P.D. and lot 771 of O.T. in the survey in Alabama and Tennessee, Seibert and DuFour[3] proposed the idea that the unpurified O.T., out of which is isolated P.P.D., may contain an additional specific factor lost during purification, or an additional nonspecific factor which enhances reactions. A supply of lot 771 of O.T. was fractionated in the usual manner. Tests on guinea pigs and in human beings failed to indicate the presence of an exceptionally high degree of specificity or of an additional specific factor in the P.P.D. lot 771. In addition to the P.P.D., two other fractions were obtained which elicited nonspecific reactions in normal animals. One of these fractions was composed of all of the original material which passed through the ultrafilter. The other fraction, chiefly polysaccharide, was obtained from the nonfilterable liquid after precipitation of the P.P.D. When these two fractions were injected into normal animals and man in concentrations of 1:2.5 or 1:5 of the original O.T., nonspecific inflammatory reactions were elicited. However, injections of the P.P.D. fraction caused no reactions. In dilutions corresponding to the usual test doses of O.T., injections of these two fractions did not cause reactions. Seibert concludes it is possible that sensitization to the nontuberculin substances in man may lead to false positive reactions, and there is evidence that these nonspecific substances may enhance the action of the specific substance of O.T., leading to much stronger reactions than those produced by the latter alone.

In considering the relative value of tuberculin testing and of x-ray in mass surveys, Douglas[4] concludes that improved methods of x-ray examination will be developed to such an acceptable point that tuberculin testing will be relegated to use as a diagnostic aid in infants and very young children and in cases of atypical lesions in adults where tubercle bacilli cannot be found. The one objection to mass x-ray without preliminary screening is the cost of making roentgenograms. The making of miniature films will solve the problems of expense.

The increasing number of reports of calcified lesions of primary tuberculosis with negative reactions to tuberculin, culminating in the report of Lumsden and his co-workers, did not go unchallenged. Long[5] in an editorial capacity clearly points out that the real issue is that of existing infection as opposed to obsolete invasions by tubercle bacilli. From a practical point of view it is not nearly as significant to determine how many persons have ever been infected with tubercle bacilli as it is to ascertain how many have been recently infected or harbor tubercle bacilli. A clear distinction must be emphasized between tuberculosis x-ray surveys and tuberculosis case-finding programs. The results of the surveys in no way cast any serious doubts over the efficacy of tuberculin as a mechanism for detecting ordinary cases of tuberculosis. On the other hand, repeated experience over a period of thirty years demonstrates conclusively that the overwhelming majority of patients with frank tuberculosis are positive to tuberculin, and too, that they react to small doses and to most of the various types of tuberculin on the market. According to Long, the fact that allergy may be absent in the presence of calcified lesions is not surprising; in fact, it would not be surprising if the tuberculin reaction eventually became negative in all cases of calcified primary lesions, provided no further infection occurred. He bases this conclusion on the observations of complete healing, with eventual sterility of spontaneous human lesions, as demonstrated by Feldman and Baggenstoss, and the decrescence and disappearance of allergy in infection artificially produced by bile Calmette-Guérin vaccine. With the general decline of tuberculosis in the community, and with the lessened opportunity for reinfection, it is only to be expected that an increasing number of nonreacting cases with calcification will be found. In commenting on the lack of proper standards of potency, specificity, and uniformity of tuberculin preparations, Long agrees that the Mantoux test is not perfect, but he states there is every reason to believe that forthcoming work will correct the situation.

In a discussion of the problem of loss of sensitivity to tuberculin, Long[6] quotes Dahlstrom who studied the question of waning allergy at Henry Phipps Institute. Dahlstrom studied the records of 514 families with a total of 3,919 members. Of this group, 3,290 people were examined, among whom there were 913 cases of tuberculosis (28 per cent). In the group of 3,290 examined, 2,490, or 76 per cent, reacted positively to tuberculin. During the period of study, about ten years, 276, or 11 per cent, became negative either transiently or for the remainder of the period of observation. It was determined by the study that there is a distinct correlation between the disappearance of allergy and the initial intensity of reaction and with the degree of household exposure. The stronger the original reaction, the less frequently does it revert to a negative one. Allergy tends to disappear where there is no exposure, and has an increasing tendency to persist as exposure is more

frequent. This indicates that reinfection is responsible for the maintenance of the positive reaction. A change from positive to negative reactions was fairly frequent in patients with calcified lesions of primary tuberculosis, but there were no instances in which the reaction became negative in frank cases of reinfection type tuberculosis.

It might be expected that the questioning of the merit of the tuberculin test in mass surveys by Lumsden, Goss, McKnelly, and Crimm and Short would evoke a response from Myers. One is not disappointed, for Myers[7] takes issue with Lumsden in no uncertain terms in a most logical presentation of the various factors involved in the detection of tuberculosis. It is admitted that the tuberculin test is not infallible, and that tuberculin preparations vary in potency. He indicates, however, that intensive studies now in progress by Long and Seibert promise a standardized testing substance with a dosage as effective in determining sensitivity of the tissues to tuberculoprotein as is possible to attain. If a high-grade tuberculin of recently tested potency is properly administered and properly interpreted, one misses only an insignificant number of persons who have foci of living tubercle bacilli in their bodies. The argument for the specificity of the tuberculin test is based on the following points:

1. The results from testing guinea pigs before and after inoculation with living tubercle bacilli.

2. The fact that veterinarians used the tuberculin test as the sole criterion of tuberculous infection, and tuberculosis in cattle has been reduced since 1917 to 0.5 per cent or less, in all but nine of the 3,134 counties.

3. The fact that the administration of bile Calmette-Guérin vaccine induces sensitivity.

4. The experience with 643 student nurses who were nonreactors, but who developed strong reactions to tuberculin soon after exposure to patients with contagious tuberculosis.

5. The fact that almost without exception all family contacts with a tuberculous patient are found to be reactors.

6. The fact that the tuberculin reaction in children frequently leads to the source of infections.

7. The facts presented by Ch'iu, who found that of 446 children who were reactors at the average age of 7 years, 15 per cent had become ill or had died of tuberculosis ten or more years later, whereas of 772 who were nonreactors at the average age of 6.6 years, only 1.7 per cent had fallen ill from tuberculosis in the succeeding ten years.

In the face of this evidence can one condemn the tuberculin test as a futile procedure?

Myers refutes the theory that the x-ray should be used as the sole criterion or only index of infection by stating that "the term x-ray diagnosis has become obsolete." The physical limitations of x-ray are numerous. About 12 per cent of tuberculous infections are extrapulmonary. According to Sweany, approximately 31 per cent of lesions which were detected on post-mortem examination were obscured from view on ante-mortem x-ray films. About 12 per cent of post-mortem lesions are too small or are too new to be detected by x-ray. Many lesions resorb, and others do not develop calcium deposits. It is impossible to make an etiological diagnosis from the shadow on an x-ray film. Tuberculosis is no longer present in those patients with calcified primary

lesions who have lost their sensitivity to tuberculin, regardless of the x-ray shadow. The interpretation of x-ray films is difficult and variable.

From the experience at Lymanhurst Health Center, Myers records the studies of 16,824 children examined since 1921. He concludes: "It is almost fruitless to make x-ray films of the chests of children, even though they react strongly to tuberculin, before they reach the age of adolescence. It is nearly fruitless to make x-ray films of children who react to tuberculin to find evidence of the lesions of the primary complex. Therefore, our studies have led us to look on the x-ray film of the chests of children as almost a total waste as far as tuberculosis is concerned." However, when adolescence is reached, and on into the years, every tuberculin reactor should have an x-ray of the chest annually and much more often if shadows appear which may be due to tuberculosis. In the event that such shadows appear, the diagnosis is made only by the correlation of physical examination, laboratory studies, and repeated x-ray examinations.

In concluding the controversy on the value of the tuberculin test, Dearing[8] states that the survey in Alabama and Tennessee indicated that the findings cast doubt on the epidemiologic value of the tuberculin survey for measuring the tuberculosis problem in a community. The findings, however, in no way invalidate the use of tuberculin or any of the tuberculins for case-finding and diagnostic work. He concludes that a single-dose Mantoux test with 0.0005 mg. P.P.D. is a reasonably efficient screen for case-finding programs where the cost limits the number of x-ray examinations, but the x-ray is still the basic tool in case finding work.

SIGNIFICANCE OF A PRIMARY INFECTION

In the critical review of 1938 it was concluded from the studies of Price, Braily, and Tortone that at least 90 per cent of white children infected with tuberculosis in the first five years of life may be expected to survive a tuberculous infection, and those who do succumb will be confined almost entirely to the first two years of life. In other words, except for infants, the primary infection is a relatively benign disease. In the development of the modern concept of tuberculosis, two diametrically opposed schools of thought have evolved. The first contends that recovery from a primary infection confers an immunity which in subsequent years protects the person from ordinary reinfections. The second school contends that the primary infection fails to immunize, and that it furnishes a source of virulent tubercle bacilli and confers allergy, both of which are requisites for the development of reinfection tuberculosis. By virtue of the natural evolution of the disease, the child with a benign primary infection is not immunized but rather is made ready for the development of serious reinfection tuberculosis. Arguments to support each contention continue to appear in the literature.

Ch'iu, Myers, and Stewart,[9] in an eight-year follow-up study, found that 15.02 per cent of 446 positive reactors developed reinfection tuberculosis, in contrast to 1.68 per cent of 772 negative reactors who developed clinical disease. The ratio of mortality in the two groups was 38:1. Stewart,[10] in a study of 5,747 children who entered Lymanhurst at an average age of 8.4 years with negative reactions to tuberculin, and who were followed for an average of 6.1 years, found that sixteen children acquired reinfection tuberculosis. Of 2,467 positive reactors

admitted at an average age of 9.9 years, 49 had chronic pulmonary tuberculosis on admission, and follow-up of the remaining 2,418 for an average period of 6.9 years revealed that 58 acquired reinfection tuberculosis. The incidence of newly developed pulmonary tuberculosis was 2.8 cases per 1,000 in the group of initial negative reactors, and 24 cases per 1,000 in the group of initial positive reactors. The ratio per 1,000 years of follow-up experience was 0.46 cases in the first group to 3.4 cases in the second group, or about 1:8.

Thus it appears clear that a much larger number of children with a primary infection acquire the reinfection type of tuberculosis than do those who escape the so-called benign infection. According to Stewart, 24 of 1,000 children who survive a primary infection in the first decade of life develop subsequent disseminations or reinfection during the second decade of life. This group which develops reinfection tuberculosis has been subjected to a detailed study by Zacks[11] of the Massachusetts Department of Public Health, and if the primary infection is supposed to confer immunity on those who survive, the findings of Zacks most seriously question the benefits derived from the initial encounter with tubercle bacilli. The group at the beginning of the study consisted of 536 children, 367 girls and 169 boys; 19 were in the age group from 5 to 9 years, 208 in the age group from 10 to 14 years, 285 in the age group from 15 to 19 years, and 24 in the age group 20 years and over. The study continued over a period of 2,144 person years, or an average of 4 person years. At the end of the period, 95 girls and 27 boys had died of pulmonary tuberculosis. Of the 141 living boys, 69 were under treatment at sanatoria; 19 were unimproved at home, and 53 (37.6 per cent) were well. Of the 272 living girls, 97 were under sanatorium treatment; 53 were unimproved at home; and 122 (44.8 per cent) were well. Zacks arrived at some definite conclusions from the study which should influence the character of managing all reactors who reach the age of puberty. "Tuberculous disseminations or reinfections in the second decade of life begin as minimal lesions early in the decade, spread slowly in the majority of instances by contiguity as time goes on, and show no symptoms or at most impereeptible symptoms at first. With the arrival of mid or late puberty, the lesions have advanced to such an extent as to give symptoms referable to the chest or toxic symptoms. The diagnosis is usually made with the advent of symptoms unless the lesions are discovered earlier by routine x-ray examination of tuberculin-positive children. In the great majority of instances these lesions will be found in the apices. These asymptomatic x-ray lesions, once they have been differentiated from similar nonspecific lesions which may mimic them, should be regarded as of grave importance. Asymptomatic lesions, when soft in appearance, show in general two distinct phases of behavior according to serial x-ray films; one type shows a tendency to spread, the other to retrogress. This behavior, unfortunately, cannot be told by the x-ray appearance of the initial lesions. The progressive lesions may spread slowly or rapidly and will kill the great majority of patients within two years, the duration of life depending inversely upon the extent of the lesion and the age at the time of diagnosis. The retrogressive type of lesions tends to subside during a longer or shorter interval of time, and the patient will survive puberty, the critical period for this group of patients."

From his experience in the treatment of this group of children, Zacks has decided that bed rest alone in a sanatorium does not modify the course of spreading tuberculous lesions, but that an early attack by collapse therapy may reduce the mortality rate of early asymptomatic lesions which show a tendency to spread. The mortality rate from advanced cases is not influenced by pneumothorax. The prognosis for soft early lesions is uncertain for at least ten years, and the most important factor in prognosis in the individual case is the behavior of the lesion according to serial x-ray films.

Cameron[12] relates the experience at East Fortune Sanatorium where, in a period of seventeen years, 1,114 children who were considered tuberculous were treated. Seventy-nine suffered from tuberculosis of the lungs as proved by the findings of tubercle bacilli or by indisputable x-ray findings; twenty-three were considered to have lung tuberculosis on clinical grounds; twenty-six (24 per cent) died in the sanatorium; and six children are still under treatment. Seventy were discharged and sixty-five have been traced; eight (12 per cent) have died; forty-seven (72 per cent) are alive and well; four are in poor health; and six are in a state of health which falls short of normal. In commenting on the significance of the type of disease, Cameron states that those who died showed an advanced, destructive, probably adult type of disease. The majority of the surviving tubercle-bacilli-positive children showed a definitely primary or postprimary type of disease such as pleurisy, perihilar infiltrations, and epituberculosis. The child who succumbs to lung tuberculosis in a sanatorium has usually reached the puberty or prepuberty age when the adult type of disease begins to make its appearance.

Dorothy Price,[13] from her experience in Eire, found that at 14 years of age, 30 per cent of children (1,500 tested) reacted to tuberculin, in contrast to Denmark where 56 per cent reacted at 14 years of age. However, the tuberculosis mortality rate in Eire in the age period from 15 to 25 years is more than three times that in Denmark. It is contended that the many deaths from tuberculosis in this age group cannot be due to a reawakening of a primary infection, but must arise from a primary infection which occurs after the fourteenth year. It is stated that "in recent years it has been accepted as proved that young people exposed to infection are less prone to develop pulmonary tuberculosis if they possess a positive tuberculin test and a satisfactorily healed childhood focus." Likewise, it is pointed out that if they should contract the disease, the death rate is much higher among the recently negative reactors than among the previously positive. The studies of Heimbeck and Mariette with student nurses are quoted to substantiate this contention. Those who develop phthisic lesions within a short time after the primary infection owe the reinfection to endogenous spread rather than exogenous inhalation, because of the special changes at puberty and the hard work done at that age. Likewise, the changes associated with puberty may result in the hematogenous spread of a fresh primary lesion or a recrudescence in a partially healed one. The early recognition of the primary lesion, followed by immediate treatment and subsequent supervision, will do more to lower the tuberculosis death rate than the best sanatorium treatment of the established disease. The experience with 100 girls who entered boarding school at 14 years of age and were studied for a period of five years is related. Eleven girls were reactors on

admission; sixteen girls changed from negative to positive while under observation, seven of whom had definite symptoms during their primary tuberculosis infection. The treatment of the primary infection in the adolescent consists simply of rest, the duration of which depends on the radiologic appearance and the sedimentation rate.

From the available evidence, the burden of proof appears to fall on the group which contends that the primary infection confers an immunity on children, thus protecting them from ordinary reinfections. The careful studies of Myers and Stewart and their colleagues at Lymanhurst since 1921 offer a firm premise for the conclusion that the primary infection perpetuates tuberculosis in man. Eradication is contingent on the prevention of infections and cannot be predicated on a questionable immunologic response to the initial invasion of the tubercle bacillus.

METHODS OF CASE-FINDING

Apropos of the efficacy of mass tuberculin testing, Doull[14] of Cleveland points out that although there has been a tremendous decline in mortality rates from tuberculosis, the risk for household contacts has not been appreciably reduced. From an administrative point of view, the field of action is becoming more sharply delimited, but despite this, time and money are dissipated in indirect effort. Only when a health department has isolated in sanatoria all its known open cases, when all active cases are under medical care, when the majority of all household contacts are undergoing periodic examination, including x-rays, when needy dependents are cared for by financial subsidy, then and not until then should expensive indirect methods of approach be employed. Ianne[15] recommends the routine tuberculin testing of all pregnant women as the best means of preventing infection of the new generation. He reports the experience in this work at the Santa Clara County Hospital where 805 women were tested; 41 per cent reacted positively, and unsuspected active tuberculosis was found in 1.7 per cent.

Edwards[16] relates the experience in Cleveland where tuberculin sensitivity is employed as a means of locating carriers and finding early cases of pulmonary tuberculosis in the adolescent child. In the public and parochial schools all children in the first grade are given the Mantoux test, and all the household contacts of reactors 12 years of age or over are fluoroscoped. In 1938, 224 cases of pulmonary tuberculosis were found in this manner. The Mantoux test is repeated in the students of the seventh grade, and again in the tenth grade in those previously negative or not tested. From 15 to 17 per cent react positively to 0.1 mg. O.T. in the seventh grade, and 25 per cent react positively in the tenth grade. All positive reactors are subjected to fluoroscopic examination. In 1938, fluoroscopic examination of 6,676 students was done, and x-rays revealed twenty-nine minimal and nine advanced cases of reinfection tuberculosis. It is concluded that this is an inexpensive and effective method of attack, and if continued, should make tuberculosis a relatively rare disease in about ten years.

In an evaluation of various techniques of case-finding programs, Plunkett[17] states that one should emphasize the examination of adults rather than children. The number of cases found among children under 15 years of age, examined because of contact or symptoms, was almost negligible, and it costs forty times more ($4,419.00 each) to discover a

case of pulmonary tuberculosis in this age group than among adults who are contacts or who have symptoms. The combination of a routine consultation type clinic and the x-raying of selected adult groups should provide the medium for an optimum case-finding program.

Fairfax Hall,[18] chairman of the Committee on Contact Infections of the American Academy of Pediatrics, emphasizes the function of the practicing physician in promoting health protection for children. Cooperation in every community with the program for healthy adults in contact with children in the school and in the home will result in fewer cases of childhood tuberculous infection. Periodic medical examinations of school teachers, domestic servants, and nurses will detect open cases of tuberculosis and minimize the possibility of infection of the children.

CONTRIBUTIONS OF X-RAY IN TUBERCULOSIS

Of considerable interest is the work of Levine,[19] who reports sixteen infants under 1 year of age in whom there was roentgenologic evidence of primary infection with parenchymal involvement of lung tissue before the development of a positive tuberculin reaction. In the usual concept, allergy occurs at the end of the period of incubation, and this asserts itself by a violent perifocal inflammatory reaction about the tuberculous focus, at which time the tuberculin test becomes positive. One explanation of the lack of correlation between a parenchymal lesion and the appearance of skin sensitivity is the possibility that the pulmonary signs may be a preallergic reaction, or allergy may have developed but antibodies may be held within the area of inflammation; there may be a general lack of antibodies in the young infant, or infantile skin may be hyposensitive to tuberculin.

In a study attempting to elucidate the interpretation of the roentgenologic shadows observed in primary tuberculosis, Rosenberg and Levine[20] report the findings in 1,852 different films of 584 infants under 5 years of age. In a comparison of 379 cases with negative Mantoux tests with 205 cases with positive reactions, the incidence of tracheobronchial shadows alone was 6.8 per cent in the former group and 9.2 per cent in the latter. The incidence of parenchymal shadows was 6.8 per cent in the negative reactors and 40 per cent in the positive reactors. Serial x-rays, however, demonstrated that tracheobronchial shadows persisted more than three months in 26.6 per cent of the negative Mantoux cases in contrast to 71.3 per cent of those who reacted positively. Parenchymal shadows persisted for three months or more in 50 per cent of the negative reactors in contrast to 92.4 per cent of the positive tuberculin cases. It is concluded that tracheobronchial shadows, even in the presence of a positive Mantoux test, are not pathognomonic of tuberculosis. However, parenchymal lesions in tuberculin-positive infants are tuberculous in nature in the great majority of cases.

In a study comparing the value of fluoroscopy and x-ray in the diagnosis of minimal pulmonary tuberculosis, Stiehm,[21] of the University of Wisconsin, has discovered small infiltrations in the lungs by special fluoroscopic examinations which were not visible on the usual postero-anterior x-ray film, and he is able to detect every lesion shown on the film by fluoroscopy. Ch'iu[22] likewise corroborates the value of the fluoroscope in the detection of pulmonary lesions among school children in Peiping, China.

Douglas[4] reports that the practical value of fluoroscopy is demonstrated by the finding of eighty-one cases of pulmonary tuberculosis among 4,000 Mexican laborers who were to be transported from Texas to Michigan. Part of the examination consisted of fluoroscopic examination with the newest type of portable fluoroscope.

The use of radiography or photography of the fluoroscopic image has been reported by de Abreu[23] of Rio de Janeiro, by Dormer and Collender[24] in London, and by Lindberg,[25] Hirsch,[26] and Potter, Douglas, and Birkelo[27] in this country. The foreign authors employ a 35-mm. film, and Potter has developed a technique which uses a 4×5 inch film. The equipment of the General Electric Company, with whom Potter consulted in the development of this technique, is marketed at a cost of about $7,000.00. Cost of the 4×5 film is about one-tenth that of the usual 14×17 inch film, and in x-ray surveys of large numbers of persons, this represents a tremendous saving in the cost of films. There is little loss in accuracy, in the reduction in the size of the film, for reduction appears to increase rather than decrease the detail. Surveys with the use of the miniature film are being conducted in Detroit and Chicago. In large surveys the economy of space in the storage of films is an added advantage. There is every indication that the use of the miniature film will result in an economy which will permit more extensive surveys and earlier recognition of the reinfection type of tuberculosis. The development of radiography represents another step in the progress of medicine, another useful weapon which should aid materially in the ultimate success of the battle against tuberculosis.

TUBERCULIN STUDIES

A pertinent contribution to the literature on tuberculin is that of Lincoln and Grethmann,[28] who point out the potential dangers of the tuberculin test in active or progressive lesions. The intracutaneous injection of tuberculin not infrequently results in constitutional reactions, and the authors cite case reports to demonstrate that serious focal reactions may result around existing tuberculous foci. Examples of focal reactions in the pleura and meninges, in the superficial lymph nodes, the sclerae, and the skin are reported. Although focal reactions about foci in the lungs have not been observed, it is thought that these occur. It is recommended that the initial dose of tuberculin should not exceed 0.01 mg., that a repetition of the tuberculin test in a child who is a reactor should be considered a hazardous procedure, and that some feasible method should be devised to brand a positive reactor to preclude further testing. It is also suggested that when tuberculosis is suspected because of a history of contact, fluoroscopy or x-ray should precede the Mantoux test.

Vollmer in 1937 described the patch test which possessed a reliability comparable to the Pirquet test. Since 1937 the reliability of the test has been improved by the use of a stronger tuberculin, four times stronger than the original O.T. It is applied in the patch test in the dry form. Vollmer and Goldberger,[29] in a comparative test on 417 children at Mount Sinai Hospital, found 100 per cent conformity between the patch test and the Mantoux test with 0.1 mg. O.T. Among 261 tuberculous children at the Sea View Hospital, the reliability of the patch test as compared with the Mantoux test with first strength solution of P.P.D.,

or 0.01 to 1.0 mg. O.T., was 100 per cent. One child who reacted to the second strength solution of P.P.D. failed to react to the patch test. These authors recommend that for general use in practice and for mass examinations, the patch test alone should suffice. For exact diagnostic work, it is suggested that a patch test be routinely applied, after which the negative reactors should be tested intradermally with 1.0 mg. O.T. or with second strength solution (0.005 mg.) of P.P.D. Weiner and Neustadt[30] concluded from their study that 95 per cent of the positive reactors are determined by the patch test as compared to the 0.1-mg. Mantoux test, but that two children who were negative to Mantoux tests gave false positive reactions to the patch test.

Taylor,[31] in a series of 744 cases in which the patch test was compared with the Mantoux test, using 0.1 mg. O.T., found that the patch test is equally as effective as the Mantoux test and possesses many advantages over the intradermal method. Court,[32] of Westminster Hospital, London, reports 98 per cent reliability of the patch test as compared with 1:1,000 O.T. in 210 cases. On the other hand, Peck and Wegman,[33] of the Maryland State Department of Health, in a comparative test on 880 school children, found the patch test positive in only 30 per cent of the cases positive to Mantoux tests with P.P.D., first and second strength solutions. They conclude that the patch test alone is unsuitable as a screening method for finding tuberculin reactors in school children. In endeavoring to improve the patch test, Vollmer and Goldberger substituted P.P.D. for O.T., but found it vastly inferior in comparative tests.

An allergometric tuberculin study by Vollmer, Zelson, and Rubin[34] compares the reactions to different concentrations of tuberculin in the patch test with those to different dilutions of O.T. in the Mantoux test. They found that, in general, persons who react to the weakest dilution of the tuberculin given intradermally react to the weakest solution in the filter paper patches.

The paucity of literature from the continent emphasizes another human paradox. While the people of Europe and Asia strive to destroy one another, every effort is made in this continent to preserve life and health. It is obvious that progress in preventive medicine rests in the hands of the physicians of America.

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Round Table Discussion, What's Wrong With My Child's Feet?

Chairman: Robert V. Funsten, M.D.,* Charlottesville, Va.
Associate Chairman: Lee Bivings, M.D., Atlanta, Ga.
Secretary: Edwin A. Socola, M.D., New Orleans, La.

What's Wrong With My Child's Feet?

Lee Bivings, M.D., Atlanta, Ga.

To review briefly the anatomy of the weight-bearing structures of the body, the leg, the ankle, and the foot all function as one unit. The bony structure consists of tibia and fibula, forming the hingelike joint into which fits the articular surface of the astragalus, thus transmitting the weight first to the heel, formed by the os calcis, and forward through the scaphoid, the cuneiforms, the cuboid, and the several metatarsals, all bound together by strong ligaments.

Active movement is carried on by the muscles of the leg and foot, the most important of which are the anterior and posterior libials, the gastrocnemius and soleus, the flexor longus hallucis, and the flexor longus digitorum. The other muscles, acting with or in opposition to the above-mentioned, complete the coordinating muscular mechanism which carries on the function of gait.

Schwartz[1] has described in great detail how weight is carried, in the normal foot, first on the os calcis, then along the outer border of the foot to the head of the fifth metatarsal thence inward to the head of the first metatarsal and great toe. Emslie[2] has called attention to the fact that the great toe is usually the longest in children and since it must, at one moment, carry much of the weight in walking, it is particularly important that its proper alignment be maintained.

Schwartz[1] has also emphasized the structural weakness inherent in the human foot which predisposes to pronation. First, the axis of weight-bearing of the os calcis is more than 1 cm. lateral to the corresponding axis of the tibia; second, the rounder, plantar weight-bearing surface of the os calcis favors the pronated position of the foot; and third, there may be congenital or acquired shortening of the calf muscles. Thus it would seem that the human foot is far from an ideal weight-bearing structure, even with the muscles tending to compensate for its inherent weaknesses.

Most babies are born with good feet; footprints at an early age show that. These early footprints also give a very definite idea of the ideal alignment or relationship of heel and forefoot.

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In a previous publication[3] I have classified the feet of children by the amount of pronation and abduction present. These revised groups are: normal, borderline, and weak. There is another type, pes cavus, the more extreme variety of which Lewin[4] speaks of as pes cavus pronatus, accurately describing the extreme pronation frequently seen in these feet.

In a recent review of 225 patients under 1 month of age, the feet were grouped as follows: pes cavus, 79; strong, 84; doubtful, 59; club, 3.

In following these children to the weight-bearing age, it was found that the pes cavus type showed most pronation, but that nearly all exhibited considerable pronation upon weight-bearing. At that time all seemed weak. Following them through the third year showed considerable recovery taking place in the balance of the feet (shown by the relation of the heel to the forefoot), and by the fifth year most of them had good feet. This same trend of strength (before weight-bearing), followed by weakness and then recovery to strength, is borne out statistically in a classification by ages previously published by me[3] and is also indicated by the work of Bloxsom.[5]

There are many infants with feet which appear strong but which exhibit some pronation and have an uncertain future. It is not easy to prophesy accurately the future of the young infant's foot which appears strong before weight-bearing, and even less easy to prophesy the future of those who appear very weak at that early age. One can detect varying degrees of the pes cavus type by footprinting in early infancy and accurately prophesy their future course. Clubfeet can be recognized easily very early and should be cared for by an orthopedist as soon as possible.

The question of when shoes should be worn and what types are advisable is important.

From the work of Schwartz and my own experience, it seems that all feet are predestined to pronate. Since modern society and hard surfaces tend to demand shoes, I believe that proper shoes are advantageous, especially to the infant learning to walk and for the following two or three years.

Since weight is applied first to the heel and since the question of pronation seems to depend chiefly on the position of the heel during locomotion, the question of greatest importance is whether or not the position of supination can be maintained by fit and construction of the heel of the shoe. This calls for a snug-fitting heel properly braced by counters of considerable strength and, in some instances, a lift under the medial side of the heel. It is obvious that the wide heel of most infant shoes does not meet these requirements, especially since most infants' heels are very narrow. The alignment of heel and forepart of the shoe should be similar to that of the footprint of an infant before weight-bearing. When a line is drawn through the central longitudinal axis of the heel it should come out of the forepart of the shoe near the area of the fourth or fifth toe, being lateral to the central axis of the shoe. Such a relationship of heel and forepart of the shoe tends to induce the weight of the body to pass from the heel along the outer border of the foot to the region of the fifth metatarsal, thence inward to the great toe. The forepart of the shoe should be much wider than the heel in the relation of one and one-half or two to one. The broad forepart should allow for the straight forward position of the great toe.

The combination last is much to be preferred over the stitched down type of shoe. Proper room should be allowed in the upper for the thick pad over the dorsum of many infants' feet. This can be done without sacrificing the all-important fit of the shoe around the ankle and heel. The upper should not be high enough to interfere with free movement of the foot on the ankle. The lace type is much more desirable than the strap shoe. If the shoe can be fitted well around the ankle and the instep, enough length can be allowed for growth without sacrificing support by poor fit.

White shoes require frequent polishing which causes softening of the leather and a loss of support and shape of the shoe. Patent leather breaks easily and will not stand hard wear. The sole of the shoe should be flexible enough for bending under the metatarsal area, but rigid enough to maintain shape which is so necessary for foot balance, especially during the early walking period when muscle development has not progressed far enough to prevent excessive pronation. There are several infant shoes on the market which meet the above specifications. It is difficult to understand why nearly all shoes for older children meet these requirements and yet so many infant shoes vary so widely.

For the very weak foot, a swung shoe with a wedged heel seems helpful in bringing the foot into an overcorrected position of adduction and supination until the muscles can develop to hold the foot there. For the mild clubfoot, a straight last shoe is very helpful.

Footprinting seems invaluable in recording the positions of the various parts of the foot during standing and walking and for comparison in development and therapy. Long illnesses are often disastrous to the feet, and great care should be exercised when locomotion is resumed. The function of the pediatrician in the care of the feet would seem to be to protect against abuse of the feet and to maintain normalcy in any way possible, particularly with the aid of properly shaped and properly fitted shoes.

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DISCUSSION

DR. W. R. PHILLIPS, ELMIRA, N. Y.—Are flatfeet in the negro child the result of heredity or environment?

ASSOCIATE CHAIRMAN BIVINGS.—In the study of the feet of 300 negro children, I found that up to the seventh year their feet would compare favorably with those of white children. It is probable that weak feet in negroes in later life are due to a combination of factors such as nutritional defects, improper shoes, poor health, and poor care. Some feet have been harmed by the use of artificial aids to walking. There is a great tendency for the infant to push along the inner border of the foot, thus increasing the already existing tendency to pronation. If the saddle of the infant's "walker" is raised so that the tips of the toes barely touch, there would be less danger of harm. A good amount of exercise may be obtained from a suspended swing.

CHAIRMAN FUNSTEN.—They do not harm, although they may increase the tendency to bowlegs.

DR. W. A. MCGEE, RICHMOND.—What do you think of toe-dancing?

CHAIRMAN FUNSTEN.—If the child is properly trained in the type suited to his feet, it is helpful. There are certain types of feet in which the muscles are too weak, and the results might be harmful to these. In ordinary pronated feet it is helpful because the weakness is chiefly in the tibialis posticus muscle, and if there is not a primary contracture of the achilles tendon, toe-dancing is a good thing; if there is, toe-dancing would further develop the gastrocnemius group.

DR. W. E. NICHOLSON, LOUISVILLE.—You said you thought a child should wear a shoe early. When a child first walks, he throws his feet wide apart so that he can stand up, and then gradually his feet come closer as he learns to balance. If he goes through a period of normal pronation, do you think that normal process is aided by shoes, or should he not go barefooted?

ASSOCIATE CHAIRMAN BIVINGS.—That question is the source of much controversy. Since Schwartz and others have shown that the structure of the foot is such that the center of weight-bearing of the tibia falls definitely inside that of the os calcis and the indirect pull of the gastrocnemius group both tend to favor pronation in every foot, I feel that proper shoeing, particularly during the early walking months, will tend to insure good feet for the infant. The statement is often made that primitive races had good feet because they wore no shoes. Dr. Lewin[4] makes the statement that primitive races do not all have good feet, and a physician who cared for the Indians of the mid-west told me that the Indian children, despite the fact that they walked on sand and wore no shoes, had very poor feet. It does not seem logical that the human foot with fundamental weaknesses mentioned above is likely to turn out to be a good weight-bearing structure unaided, especially when we consider the artificial environment of hard floors and paved streets. Therefore, properly designed shoes would seem a most necessary and reasonable procedure to assure foot balance.

DR. NICHOLSON.—When do you think a child's foot needs support? If the shoe is built up early you do only one thing, the foot is thrown in, and the child is likely to stumble. In due time, he will normally come to a straight line and his feet will come in.

ASSOCIATE CHAIRMAN BIVINGS.—There is no doubt that most children have good feet. However, there are some who will go into the period of weakness and not come out unaided. A wedge under the heel will make them toe in, and that is exactly what we desire in most instances because most pronated and abducted feet toe out. The pigeon-toed child can be helped best by a wedge under the heel and also a wedge under the outer front portion of the shoe in the area of the fifth metatarsal joint. The time to add the wedges is after the child has worn the first walking shoes long enough to see whether or not there is any running over of the inside of the shoe. And only those shoes that "run over" are built up. There is no doubt that foot balance, established by proper shoes, promotes earlier walking especially in the badly pronated foot.

DR. MCGEE.—Will you discuss flexibility of the soles and the time for heels to be added to shoes.

ASSOCIATE CHAIRMAN BIVINGS.—Flexibility of the soles has been overemphasized. The sole must be sufficiently rigid to maintain shape if the shoe is to be of any value in maintaining foot balance. It would seem that the only place where flexibility matters is under the ball of the foot, and the shoes described as desirable types assure that feature and still retain the shape of the shoe after months of wear.

CHAIRMAN FUNSTEN.—As soon as there is an established definite flatfoot tendency, there should be some heel. It relieves the general strain on the foot.

DR. A. C. GIPSON, GADSDEN, ALA.—When should a child be allowed to wear sandals, oxfords, or tennis shoes?

ASSOCIATE CHAIRMAN BIVINGS.—If a child has an obviously strong foot, it doesn't matter. The child should pass the 3-year age mark because no one can tell very definitely before that age what kind of feet a child will have. Wearing tennis shoes, sandals, and being barefooted are all in the same category. None support the foot. If the feet are weak, they need support, and increasing weakness may be a result of going barefooted. It does not seem logical that an already weakened weight-bearing structure could improve while bearing weight and without help.

CHAIRMAN FUNSTEN.—When mothers ask whether their child should be allowed to go barefooted, depending on the condition of the feet, I usually tell them it is perfectly all right except on hard surfaces.

ASSOCIATE CHAIRMAN BIVINGS.—Proper shoeing is a prophylactic measure in the normal infant. Obviously the shoes must allow sufficient room for growth, and that can be accomplished in the desirable type shoes by fitting the heel and forefoot, yet allowing ample length for growth. Tight-fitting socks can do much harm in hampering growth.

DR. A. L. RICHARDSON, DETROIT.—I have the feeling that the shoe salesman and physician tend to err on the side of a too rigid shoe for the runabout child. Our grandmothers wore whalebone corsets, and in that generation nearly all the women complained of weak backs. They did not develop the lumbar group of muscles. Our women of a decade or so ago started wearing high heels without ankle support, and we men were more or less critical and told them they shouldn't cross a street for they would surely sprain an ankle. The orthopedists have not had many jobs from those ankles; in fact, the women today have much stronger ankles than their mothers because those ankles have developed as a result of lack of support. The rigid type of shoe tends to do much the same thing to the foot as the corset did to the back.

ASSOCIATE CHAIRMAN BIVINGS.—It is true that a properly designed shoe can be sufficiently rigid to maintain shape and yet flexible enough around the ankle and under the metatarsal arch to allow freedom of movement necessary to normal locomotion. Muscular action concerned in walking is chiefly derived from the leg muscles and therefore would not be hampered by a well-designed shoe.

CHAIRMAN FUNSTEN.—Dr. Richardson's argument about the corsets is very interesting, but it does not apply exactly to feet. If we could presume that a child was going barefooted all his life and would walk on soft surfaces and not on wood and concrete, it might be all right to let him loose to develop as he could. A child can mold his toes in the sand to get some exercise, which he cannot do on hard floors. We are going through a transition period with our feet, and do not have the strength in them that we used to have. Men are still reasonably sensible about shoes, but women still are not, and while their ankles are perhaps withstanding the gaff of the high heels, it is certainly true that we have more sprained ankles than ever before. It is more important for a child to keep a good contour and a normal shape of the bone during the developmental stage, to have them develop normally, and to have the ligaments rigid rather than relaxed. You must consider some support during the rapid growth period. It is also true that some children's bones outgrow the development of their muscles and their feet give down as a result, so that we are not going to lose anything during this period of rapid growth if we keep these children under control.

DR. H. W. WILLIS, MIAMI, FLA.—The weak foot is usually seen in malnourished children and the condition improves with correction of nutrition.

CHAIRMAN FUNSTEN.—It is definitely true that malnutrition plays an important part in the weaknesses of the foot and ankle. Some children are so malnourished they cannot get on their feet, although there may be no paralysis. They do tend to improve with exercise, and, if necessary, we can resort to artificial exercise with apparatus or massage. Exercises in older children are comparatively simple. The following set of six exercises can be mimeographed and given to the parent:

The first exercise, for the flexors of the toes, which are of part the support of the arch, is to stand with the heels just on the long edge of a towel and gradually draw the towel underneath the arch by working the toes.

The second exercise is to stand on the outer side of the foot, then the other side of the foot, and at the same time to flex the toes under the arch as far as possible. You will find frequently where there is a metatarsal arch strain that these children can hardly do this at first, but gradually will improve to a point of efficiency.

The third exercise is to rise on the ball of the foot, evert the ankle slightly and then come down again into the normal position.

The next exercise for stretching the tendon achilles and for improving the strength of the tibialis anticus is to rise on the heels and to invert the foot in that position.

Many exercises for the metatarsal arch can be devised, such as picking up marbles or pencils, and it is usually interesting for children to do this type of work. This result is brought about in the exercise of rising on the ball of the foot and everting the ankle.

The gluteals are decided outward rotators and gluteal exercises probably are just as useful as having the child lie on his face and raise the legs backward rhythmically, one then the other. Gluteal exercises should not be given unless some form of abdominal exercise is given with them. Children frequently have a combination of lordosis and potbelly, and abdominal exercises, leg raising in the prone position, and coming to the sitting position from the prone position are important.

DR. LETA J. WHITE, PETERSBURG, VA.—Are most flatfeet the result of rickets?

CHAIRMAN FUNSTEN.—Many rachitic cases have high arches with prominent box ankles and box knees and other evidences of the rachitic syndrome.

DR. R. C. HOOD, CHILDREN'S BUREAU, WASHINGTON, D. C.—What type of shoe is best for the infant with a fat ankle?

ASSOCIATE CHAIRMAN BIVINGS.—This shoe which I have described is designed to allow room for the fat pad on the dorsal surface of the foot and around the ankle. If the shoe is laced tightly while the child is standing, there is little danger of getting it too tight.

DR. J. K. GLEN, HOUSTON.—Orthopedists often use inlays in shoes to correct pronation. Is this a good measure?

CHAIRMAN FUNSTEN.—In pronated feet the weight-bearing should be shifted from the inner side of the astragalus to more nearly the center, and the easiest way is by a lift under the heel. Ability to split the sole and insert a wedge of leather of the desired thickness wherever it may be needed is another reason for preferring the Goodyear welt to the McKay or turn shoe.

DR. P. C. ELLIOT, NASHVILLE.—Discuss the treatment of pigeon-toes. When should treatment be instituted?

CHAIRMAN FUNSTEN.—If the condition is so severe as to cause stumbling, treatment should be started at once. A lift under the medial side of the heel and another under the outer surface of the shoe in the region of the little toe usually will cause the child to evert the feet. If the condition is sufficiently severe, elastic rotators may be used.

DR. D. GABERMAN, HARTFORD, CONN.—If an older child has a flatfoot, what is the plan of correction? Are steel arches still used?

CHAIRMAN FUNSTEN.—The rigid steel supports tend to cause atrophy of the muscles. If the child is old enough to take exercises, I should depend more on such a regime than any kind of support.

DR. E. T. MCENERY, CHICAGO.—How should one correct familial overriding toes?

CHAIRMAN FUNSTEN.—There is a small aluminum brace which goes over the high toe and under the adjacent toe which will correct the trouble if it is worn long enough. Adhesive tape can be used the same way. Finally, osteotomy of the middle phalanx of the toe will really correct it.

DR. H. J. STARR, CHATTANOOGA.—Do you advise using sponge rubber in support of flatfeet?

CHAIRMAN FUNSTEN.—Sponge rubber has many advantages; we usually use felt padding which gradually flattens down, thus decreasing the amount of push.

DR. T. P. SALTEIL, CHICAGO.—Do you prescribe any different care in the overweight child under 2 years of age than in the normal child of the same age?

ASSOCIATE CHAIRMAN BIVINGS.—That would be an individual problem. The usual big baby has enough strength to take care of added weight. I remember one infant of 7 months weighing 27 pounds and walking. She had and does have good feet.

DR. SALTEIL.—What part does heredity play in the formation of the feet?

ASSOCIATE CHAIRMAN BIVINGS.—It plays a very important part. For instance, in the pes cavus type, all are hereditary. However, actual weakness may be predisposed by the shape of the feet, but nutrition, foot imbalance, and many other factors actually cause bad feet. One might safely say that the long narrow foot which is hereditary is much more likely to break down under strain than the short chubby foot. Pes cavus is hereditary and often causes foot strain and painful feet because of marked pronation. Yet, strictly speaking, it is not a weak foot.

QUESTION.—What is the treatment of a bunion in a young girl?

CHAIRMAN FUNSTEN.—It is doubtful if a bunion would be severe enough in a young girl to justify any operative procedure. A sufficiently wide shoe and some protection of the metatarsal arch, with exercises to develop the muscles of the metatarsal arch which have possibly played an important part in the formation of the bunion, would be advisable. If the child has reached 15 or 16 years of age, then operation would be more advisable.

DR. M. V. ADAMS, MOBILE, ALA.—At what age should a child begin to wear hard-soled shoes?

ASSOCIATE CHAIRMAN BIVINGS.—The hard-soled shoe is the only one that will give the child any help at all. The important age should be when he first begins to walk; if you give any support at all, he certainly would need it then. The hard-soled shoes should not be so stiff that they will not be flexible under the metatarsal arch, which is the only point where flexibility is particularly important.

DR. W. B. RAYCRAFT, OAK PARK, ILL.—What about low shoes? At what age may the child go barefoot?

ASSOCIATE CHAIRMAN BIVINGS.—A child should wear high shoes for about the first two years. After that time, it doesn't matter particularly.

If the foot is normal and the child is walking on some soft surface, going barefoot is not harmful, but if the child has a weak foot, he should never be allowed to go barefoot.

Dr. Lewin goes even so far as to say that a child should never wear bedroom slippers. Whether or not we approve, our babies are going to wear shoes, and it seems to me very important and very essential that they wear the right kind of shoe.

DR. SUZANNE S. SCHAEFER, NEW ORLEANS.—What indications are there for arch supports inside the shoe?

CHAIRMAN FUNSTEN.—If a child's foot is definitely flat, arch supports should be used at least temporarily. There is a great difference of opinion about what constitutes the proper type of arch support. For the very severe cases in children of the asthenic type, a very rigid support may be necessary over a period of time. The shoe may be built up on the inside curve, with leather starting on the ground.

If the foot is pronated without any flattening of the arch, there is no indication or purpose in using an arch support, because the difficulty is not in the arch, but in the ankle or the joint below the ankle rather than in the arch itself. We have used a medium firm felt for an arch support; we get the design for the arch directly from the weight-bearing surface of the foot, and the purpose of the arch is to distribute the weight equally throughout the entire weight-bearing surface of the foot and to add a little additional lift under the scaphoid bone. If the strain is in the metatarsal arch, then we add a metatarsal bar.

We feel that the continuous use of arch supports is not advisable in all instances, and we get away from it by giving these children certain forms of exercises, beginning as soon as they are old enough to learn the idea. Sometimes the mothers have to get as much of the exercise as the children do. The idea always is to build up muscle power so that this, rather than any support, will take care of the arches.

DR. H. R. ROEHM, BIRMINGHAM, MICH.—Do you think that pronation of the feet is physiologic and occurs normally from 1 to 3 years?

ASSOCIATE CHAIRMAN BIVINGS.—The natural shape of the human foot is such that some pronation is a result of its inherent imbalance. The foot goes back to normal again as the muscles develop to support that foot.

DR. W. D. BROWN, BEAUMONT, TEXAS.—What percentage of feet found to be flat from birth can be counted on to correct themselves without orthopedic interference?

CHAIRMAN FUNSTEN.—The foot that is actually flat at birth is probably a distinctly orthopedic problem. Some of the extreme ones that are congenital flatfeet

should be corrected by plaster casts, just as one would correct the opposite deformity, a clubfoot. Arches can be built up and exercises can be instituted which would probably take care of the milder types.

ASSOCIATE CHAIRMAN BIVINGS.—It doesn't matter particularly whether or not we put any shoes on the babies before they start to walk. Any kind of foot covering that will keep the feet warm will answer.

DR. G. C. MALLEY, ZANESVILLE, OHIO.—What are some of the more common symptoms of bad feet, particularly those simulating rheumatic fever pains?

CHAIRMAN FUNSTEN.—The symptoms may be either in the foot itself, or in the calf muscles, or the leg muscles. The static type of pain from the weak arch gradually increases as fatigue increases.

DR. D. C. MEBANE, TOLEDO, OHIO.—What is the proper technique in examining an infant's or a child's foot?

CHAIRMAN FUNSTEN.—The child should stand firm facing the examiner. You can see then how much pronation is in the ankle, how much abduction or adduction is in the forefoot, and the amount of flattening in the longitudinal arch. Run your finger along the inner border of the foot. You can feel whether the bone is actually down or whether it's a fat foot. Then have the child turn with his back to you. You can note very readily the amount of pronation, particularly if it should be the reverse deformity.

The child should then be made to raise his forefeet off the floor, standing on the heel. This is to tell whether or not there is any contracture in the gastrocnemius. Then have him stand on his toes. The child is then put on the table, and you feel the flexibility of the various joints of the foot. Some feet are abnormally flexible; some are rather stiff. The stiff type, naturally, is usually the stronger, although deformities may be present. The condition of the muscles of the leg should be particularly noted—whether they are developed, or if they are flabby and loose. It may be part of the trouble. You feel about the metatarsal head, particularly to see if there is any tenderness there. Sometimes these children are actually suffering from a metatarsal arch strain rather than a longitudinal arch strain, and your efforts to correct the thing must be directed toward that arch rather than toward any lifts or wedges that might be used to correct the longitudinal arch.

You ask the child to stand on the outer sides of his feet, and pull his toes down under to see what the power of correction they automatically give. Ask him to walk around a little that way.

DR. P. ROSENBLOOM, CHICAGO.—What is the average length of time a baby can wear a properly fitting shoe? In other words, what is the rate of growth of a child's foot?

ASSOCIATE CHAIRMAN BIVINGS.—If the heel and instep are properly fitted, one can allow a full fingerwidth extra length to take care of growth. Usually that means that the child can wear the shoes for three months without crowding.

DR. L. B. VAUGHAN, LONG BEACH, CALIF.—Please discuss arch supports commonly sold.

ASSOCIATE CHAIRMAN BIVINGS.—They do not allow for any variation in the individual foot. As a rule, they are made of a metal, and the use of rigid supports is contraindicated in all cases except the extreme myasthenic case during the

early stages of treatment. The best way of determining what the child needs is through examinations which have been described, and the pedograph. A support designed directly from that pedograph should be constructed.

DR. HUGHES KENNEDY, JR., BIRMINGHAM, ALA.—Explain in detail the placing and size of a wedge.

ASSOCIATE CHAIRMAN BIVINGS.—The size of the wedge depends on the size of the shoe and the age of the child, and the width or height of the wedge varies anywhere from ⅛ to ¼ inch.

DR. BROWN.—Discuss harmful effects, if any, from too early encouragement of walking.

ASSOCIATE CHAIRMAN BIVINGS.—The best criterion to follow is to let the baby come to it himself. Overweight or early walking is not harmful if the child is normal muscularly and in every other respect.

News and Notes

Many pediatricians are not familiar with the **Society for Research in Child Development**, which was organized in 1933. Membership is $5.00 yearly, and is open to any person interested in child development and the care of children. The dues cover subscription for the current year to several publications: *Child Development Abstracts and Bibliography*, a bimonthly journal containing information about current research and publications; *Child Development*, a quarterly journal containing specialized original articles on research; *Monographs of the Society*, published irregularly in one volume annually. The publications are all of outstanding merit, and the abstracts and bibliographies make available the resources of publications in this field. The headquarters of the organization are at the National Research Council, 2101 Constitution Ave., Washington, D. C.

Dr. Joseph Brennemann has been appointed Professor of Pediatrics and Head of the Department at the Southern California University Medical School. He is also Medical Director of the Children's Hospital, 4614 Sunset Blvd., Los Angeles.

Book Reviews

Methods of Assessing the Physical Fitness of Children. Rachel M. Jenss, Sc.D., and Susan P. Souther, M.D. Publication No. 263 of the Children's Bureau, Supt. Documents, Washington, D.C. Price, 15 cents.

This publication is the report of a study made in New Haven, from 1934 to 1936, in which it was attempted to determine the value of various indices of body build used to estimate the physical fitness of children. As one part of the study, a group of 713 7-year-old children were examined by a pediatrician who classified them as to their nutritional conditions by an estimation, according to a fixed classification, of the color, muscle tonus, and amount of subcutaneous fat. Careful anthropometric measurements of the children were made and their classifications were determined according to the Baldwin-Wood tables, the A C H index, the Nutritional Status indices, and the Pryor Width-Height tables. As might have been expected, little correlation was found between the pediatrician's findings and the various indices, or between any two of the indices. The indices failed to prove an effective method of identifying children who, according to the criteria used by the physicians, were likely to be physically unfit. Within the limitation of the study, the work was carefully done and checked. The report may prove useful in helping stop the use of measurements as a method of determining physical fitness. Such mass measures served a purpose in the early days of the child hygiene movement, but measurements alone as a method of determining physical fitness, without consideration of such things as individual heredity and race, as well as the much more important matter of functional capacity and ability, which after all is perhaps the best test of physical fitness, have long been recognized as unsatisfactory and of little value by pediatricians. The study intentionally left out these critical matters as the plan was to test the indices in the way they are commonly used to determine fitness, or rather nutritional condition, in school children. It is to be hoped that the report will have a widespread distribution among school health workers, and that sooner or later the truth will be learned that simple mass measures are of little or no value in determining the physical fitness of the individual.

The Doctor and the Difficult Child. William Moodie, M.D., F.R.C.P. New York, 1940, The Commonwealth Fund, pp. 214. Price $1.50.

In this small volume by Dr. Moodie, Medical Director of the London Child Guidance Clinic, the subject of child guidance for the physician is better and more clearly presented than in any other book with which we are familiar. It is a book that should be read by pediatricians and particularly by those who are planning to specialize in pediatrics. Dr. Moodie starts with the recognition, the study, and the treatment of the problems in general, and then discusses some eighteen specific behavior problems, such as stealing, truancy, backwardness, enuresis, sex problems, and psychoses. As the author states, the book is rather an informal discussion of the fundamental disturbances of behavior or personality rather than a purely scientific treatise, and it is just this that makes it of so much value to the pediatrician. The chapter on treatment is essentially sane and full of common sense, and the author avoids discussion of the various controversial schools of thought, although it is obvious that he is fully cognizant of their ideas and methods. Pediatricians who

have long recognized the importance of child psychology and child guidance in their daily work have been looking and waiting for a book like this for many years. The Commonwealth Fund has done a great service in publishing Dr. Moodie's book at a price which makes it possible for the younger pediatrician to add it to his personal library.

Born That Way. Earl R. Carlson, M.D., New York, 1941, The John Day Co. Price $1.75.

This book is the autobiography of Dr. Carlson who was handicapped from birth with spastic paralysis as a result of a birth injury. His struggles for adjustment and for an education which eventually took him through medical school are related in a simple, moving way. The problems of the handicapped, both physical and psychologic, are brought out clearly in the telling of the story. Since graduation, Dr. Carlson has devoted his time to working with the spastic. The story shows how determination can and will help the handicapped individual to overcome his physical difficulties and make life worth while, not only for himself, but for others. It is a book to be recommended to the parents of handicapped children, and to the handicapped himself when he reaches the age where realization develops of the problem he must face throughout life.

Hospital Formulary. University of California, 1941, Berkeley and Los Angeles, University of California Press, pp. 270. Price $2.00.

In a small volume of about 4 by 7 inches, clearly printed on thin paper so that the book is only ⅜ inch thick, a committee of the medical faculty has compiled an enormous amount of material in regard to drugs, vaccines, sera, fluids for parenteral injection, vitamins, etc., as well as tables of laboratory data, laboratory and clinical procedures, emergency, acute poisoning, and the like, for use of the hospital staffs and students. It is splendidly suited to be slipped into the physician's bag. It is in many respects the most satisfactory of the many books of a similar nature which have been prepared by hospital and teaching centers.